KING'S COLLEGE LONDON

Monitoring Physiological Trajectories

A Transfer Report by

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Abstract

Clinical deteriorations of hospital patients must be recognised early to maintain patient safety and minimise treatment costs. Currently early warning scores are calculated several times each day to warn of potential deteriorations. A score is calculated using parameters measured at one particular time. In contrast, clinicians often use physiological trends over time to improve their assessment. Therefore, we hypothesised that:

Deterioration of inpatients could be detected earlier by monitoring their physiological trajectories.

To test this hypothesis, we have constructed a database of patients' physiology throughout their hospital stay after cardiac surgery, including continuous ECG and pulse oximetry signals. Data timestamps were misaligned during acquisition, so an algorithm has been developed to correct for this. Artefactual data was removed using signal quality indices. Initial physiological trajectories were calculated using Gaussian processes.

We have implemented algorithms to estimate respiratory rate, a key indicator of deteriorations, from these signals. We have evaluated their precision in a cohort of healthy subjects. Preliminary results suggest that they are more precise in younger subjects. Therefore, further work is required to determine whether they are sufficiently precise for use with the patient population.

We have identified indices of cardiovascular function which can be derived from these signals for detection of deteriorations. We hypothesised that the variability in cardiovascular state in the hours after surgery may indicate the class of trajectory which a patient is likely to follow. Therefore, we derived and evaluated the precision of cardiac output algorithms to determine their precision during changes in vascular state. Preliminary results suggest that more complex algorithms are required.

Finally, we have identified the remaining steps required to test this hypothesis.

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Abbreviations

FM	**A**mplitude **M**odulation
ABP	**A**rterial **B**lood **P**ressure
ADC	**A**nalogue-to-**D**igital **C**onverter
AF	**A**trial **F**ibrillation
AMU	**A**cute **M**edical **U**nit
bpm	**b**reaths (or **b**eats) **p**er **m**inute (as appropriate)
FM	**B**aseline **W**ander
CABG	**C**oronary **A**rtery **B**ypass **G**raft
CO	**C**ardiac **O**utput
ECG	**E**lectro **C**ardio **G**ram
EPR	**E**lectronic **P**atient **R**ecord
EWS	**E**arly **W**arning **S**core
FFT	**F**ast **F**ourier **T**ransform
FM	**F**requency **M**odulation
GCS	**G**lawsgow **C**oma **S**core
HDU	**H**igh **D**ependency **U**nit
HF	**H**igh **F**requency
HR	**H**eart **R**ate
HRV	**H**eart **R**ate **V**ariability
ICU	**I**ntensive **C**are **U**nit
LF	**L**ow **F**requency
LISTEN	Study monitoring patients post-cardiac surgery
LOC	**L**evel **O**f **C**onsciousness
LOS	**L**ength **O**f **S**tay
MET	**M**edical **E**mergency **T**eam
MEWS	**M**odified **E**arly **W**arning **S**core
NEWS	**N**HS **E**arly **W**arning **S**core
NICE	**N**ational **I**nstitute for Health and **C**linical **E**xcellence
NHS	**N**ational **H**ealth **S**ervice
OR	**O**dds **R**atio
PDF	**P**robability **D**ensity **F**unction
PPG	**P**hoto**p**lethysmo**g**raphic Signal
PPGV	**P**hoto**p**lethysmo**g**raphic **V**ariability
PPV	**P**ositive**P**redictive**V**alue
PWV	**P**ulse **W**ave **V**elocity
RIIV	**R**espiratory **I**nduced **I**ntensity **V**ariation
RMSE	**R**oot **M**ean **S**quare **E**rror
RR	**R**espiration **R**ate
RSA	**R**espiratory **S**inus **A**rrhythmia

SBP	**S**ystolic **B**lood **P**ressure
SD	**S**tandard **D**eviation
SEM	**S**tructural **E**quation **M**odelling
SQI	**S**ignal **Q**uality **I**ndex
SpO2	Blood oxygen saturation
temp	**temp**erature
TPTDCO	**T**ranspulmonary **T**hermo**D**ilution **C**ardiac **O**utput measurement
VORTAL	**V**alidation **o**f **R**espiratory Ra**t**e **Al**gorithms
ViEWS	**Vi**talPAC **E**arly **W**arning **S**core

Chapter 1

Introduction

The burden of preventable inpatient clinical deteriorations has been widely reported and tackled during the past fifteen years [1–3]. In this chapter we present evidence from the literature to support the hypothesis:

> Deterioration of inpatients could be detected earlier by monitoring their physiological trajectories.

We define deteriorations as rapid worsening of health, inpatients as patients residing in hospital, a physiological trajectory as the physiological state of an individual as a function of time, and physiology as bodily function.

In this chapter, firstly we overview the importance of early recognition of deteriorations. Secondly, current methods for detection of deteriorations of inpatients are described. Thirdly, we overview how physiological trajectories have been used previously. Fourthly, we outline how monitoring physiological trajectories could lead to earlier detection of deteriorations. We conclude with a description of the goal of the PhD research and an overview of this transfer report.

1.1 The Importance of Early Recognition of Deteriorations

Early recognition of deteriorations is important to improve patient safety, health economics, and the well-being of other stakeholders such as visitors and staff.

Early recognition of deteriorations can improve patient safety. In the early 2000s, it was estimated that in the UK 23,000 cardiac arrests and 20,000 unanticipated Intensive Care Unit (ICU) admissions were preventable [3]. It was proposed that the incidence of such events could be reduced by recognising and acting on the preceding changes in physiology [1, 4, 5]. Subsequently, early warning scores (EWSs) were developed to allow timely recognition of such patients and subsequent prevention of adverse events. The use of EWSs was recommended across the NHS in 2012 [6], facilitating improved patient safety [7].

Preventable deteriorations amount to significant healthcare costs. In the UK clinical negligence costs for the NHS totalled 769 million during 2008-2009 [8]. In the USA adverse events have been estimated to cost upwards of US$17 billion [9], and in Australia they have been estimated to account for 8% of hospital bed days [10]. Complications after surgery increas length of stay (LOS) [11–13], increasing treatment costs. Therefore, early recognition and subsequent prevention of deteriorations should improve healthcare economics.

More broadly, deteriorations affect relatives, and are distressing and demoralising for staff [8].

1.2 Detection of Deteriorations

EWSs are calculated manually from routinely measured physiological parameters. An elevated score indicates that a patient has abnormal physiology, and may be at risk of deterioration.

1.2.1 Deteriorations are Preceded by Changes in Physiology

EWSs are based on the assumption that deteriorations are preceded by changes in physiology. This is well supported by physiological data collected prior to deteriorations. Schein *et al.* published landmark results in 1990 that 84% of patients *"had documented observations of clinical deterioration or new complaints"* in the eight hours preceding cardiac arrest [14]. This was supported by a study by Franklin *et al.* [15]. Later, physiological abnormalities were also observed prior to unplanned admission to ICU [16] and preventable deaths [17]. It has been independently confirmed that evidence of deterioration can be observed 8-12 hours before deterioration [5, 18]. Furthermore, Alvarez *et al.* found that out of 14 electronically collected predictors of resuscitation events and death, 9 were physiological (and at least 4 of the remaining 5 are directly linked to physiology) [19]. The assumption is also supported by expert opinion. In 2010 a

consensus of international experts found that cardiac arrests and deaths are mostly preceded by physiological parameters *"lying outside ... normal ranges"* [20]. The overwhelming conclusion is that physiology changes prior to most deteriorations.

1.2.2 Early Warning Scores

EWSs are now in use worldwide [21, 22]. They are still being developed, and as of 2010 at least 34 different EWSs had been proposed [23]. A history of EWSs is given in Appendix A. EWSs have been shown to correlate with important patient-centred endpoints such as levels of intervention [24], higher hospital mortality [24, 25], length of stay [25], and to be a better predictor of cardiac arrest than individual parameters [26]. In practice, they have resulted in clinical response at lower levels of physiological abnormality [27].

However, it has not been shown conclusively that the use of EWSs translates to improved patient outcomes [28]. For instance, in 2003, a study of the use of an EWS to triage medical admissions did not impact outcomes [29]. In 2007, there was *"little evidence of reliability, validity and utility"* of EWSs [30], particularly as the majority of 33 different EWSs discriminated poorly between survivors and non-survivors [31]. Reassuringly, since then a single EWS, the NHS EWS (NEWS), has been recommended for use across the NHS, and has been shown to outperform the 33 previously tested EWSs [32].

The components of EWSs are illustrated in Figure 1.1, and described below.

FIGURE 1.1: The components of an Early Warning System: (i) Physiological measurements are used as inputs; (ii) an overall EWS is calculated; (iii) the EWS is outputted indicating physiological state and therefore the risk of clinical deterioration; (iv) this can trigger a clinical response.

Physiological Parameters

The physiological parameters used as inputs to NEWS are:

- Respiration Rate (RR)

- Blood Oxygen Saturation (SpO2, the ratio of oxyhaemoglobin to total haemoglobin in arterial blood [33])
- Temperature (temp)
- Systolic BP (SBP)
- Heart Rate (HR)
- Level of Consciousness (LOC)
- Administration of supplemental oxygen (dichotomous)

Evidence for the use of each parameter is given in Appendix B. These parameters can be easily measured at the bedside using routine monitoring equipment (an 'observations monitor'), consisting of a pulse oximeter, thermometer and sphygmomanometer (Figure 1.2). Additional consideration of non-routine variables such as urine output, biochemistry and haematology results has been recommended under certain circumstances [20].

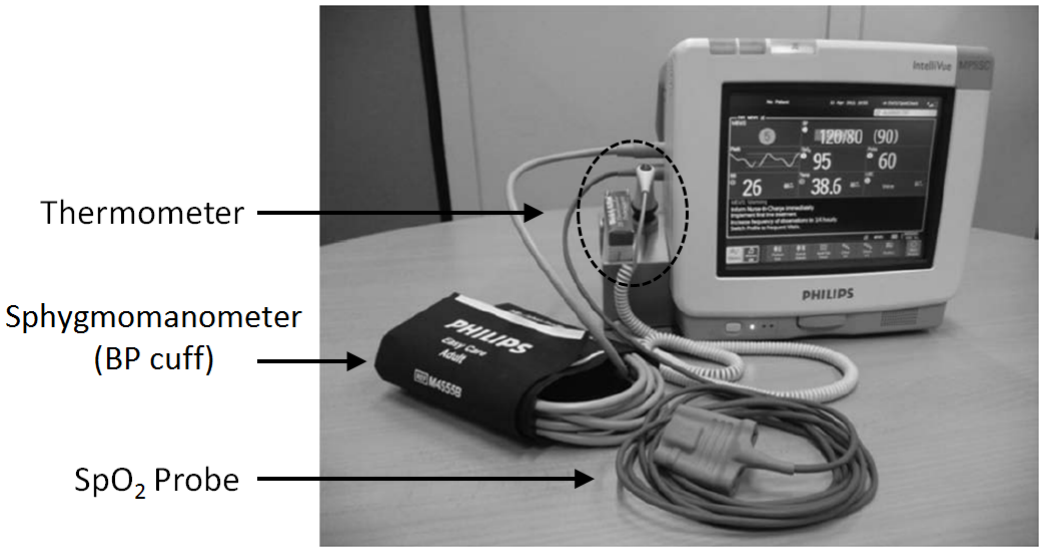

FIGURE 1.2: Philips Observations Monitor, with sensors labelled. (Adapted from [27])

NEWS observation data is collected a minimum of every 12 hours, and mostly every 4-6 hours with acutely-ill inpatients [6]. In 2004, the *"urgent need"* for research into the optimal frequency of measurements was highlighted [34]. Yet, in 2010 this remained an open question [20], which will be addressed in this PhD.

The frequency with which parameters (and therefore NEWS) are measured could be increased. Indeed, the aforementioned consensus of experts agreed that *"if practical and affordable, all*

patients should be monitored continuously" [20]. Furthermore, *'even with 4-hourly observations, as many as 94% of the occurrences of significant clinical deterioration ... could be missed'* [35, 36]. Increased frequency would improve patient outcomes in two ways: (i) deteriorations which progress rapidly and would otherwise be missed between routine observations could be detected; and, (ii) deteriorations would be detected earlier [20, 37, 38]. Wireless sensors are improving rapidly and may now be a viable method for monitoring inpatients continuously. We will investigate the potential for continuous monitoring to provide earlier detection of deteriorations.

EWS Calculation

The introduction of NEWS brought about a standardisation of the calculation of EWS across the UK. Beforehand, many different algorithms (variations on the same theme as NEWS) were used to calculate EWS, such as the 18 quoted in [39], and the 33 tested in [32]. The procedure for calculating NEWS is [6]:

1. Convert each physiological parameter to a score (0-3, ranging from normality to abnormality). For instance, a HR of 100 bpm is slightly elevated from a normal range of 51-90, so it is assigned a score of 1.
2. Sum the individual scores to calculate an aggregate score.

Outputs and Action

Assessment of clinical risk using NEWS is based on the finding that no single parameter is all-important. For instance, Bleyer *et al.* found that a single abnormal parameter was associated with a mortality of 0.92% in their cohort, whereas this figure rose to 23.6% when three parameters were abnormal [40]. Therefore, aggregate scores of 1-4, 5-6 and ≥ 7 indicate a low, medium and high clinical risk respectively. In addition, an individual parameter score of 3 indicates at least a medium clinical risk. Assessment of clinical risk using NEWS informs a graded response, as recommended by the Royal College of Physicians [6] and summarised in Table 1.1.

Approximately 10% of observation sets collected from patients in an acute medical unit (AMU, where acutely-ill patients are cared for on admission to hospital) or medical ward are expected to show medium clinical risk, and 10% a high clinical risk [6]. On a surgical ward 10% are expected to show a medium clinical risk or higher.

TABLE 1.1: Graded responses to clinical risk assessment by NEWS.

Risk	Monitoring Frequency	Additional Response
NEWS = 0	$\geq$ 12 hourly	none
Low	$\geq$ 4-6 hourly	Nurse to assess patient and consider increased frequency of monitoring and / or escalation of care.
Medium	$\geq$ hourly	A clinician trained in assessing acutely-ill patients to assess patient urgently.
High	continuous	A clinical team with critical care competencies to conduct an emergency assessment. Consider transfer to high dependency unit (HDU) or ICU.

Medical emergency teams (METs) have been introduced over the past 15 years to respond rapidly to clinically unstable patients [41]. They are called by ward staff, typically for a patient with a medium or high clinical risk. Early studies found that a MET can *"significantly reduce the incidence of and mortality from unexpected cardiac arrest"* [41], and *"may be associated with fewer cardiopulmonary arrests"* [42]. However, a randomised controlled trial found that the MET system *"does not substantially affect the incidence of cardiac arrest, unplanned ICU admissions, or unexpected death."* [43]. Therefore, evidence of the effectiveness of METs is not conclusive.

1.2.3 Potential Improvements to Early Warning Scores

It is clear that the performance of EWSs could be improved. Most suggestions for improving EWS focus on their effectiveness. For instance, Luettel *et al.* identified ten failure points in the process of recognising and responding to deteriorating patients, which could be summarised as non-compliance with the processes in which EWS is used [44]. However, even the efficacy of EWSs is far from ideal. For instance, EWSs have low sensitivities [20, 45], and are late indicators of deterioration since they have been developed and validated using endpoints late in the deterioration process [32]. Alvarez *et al.* demonstrated the potential for improved efficacy by retrospectively developing and testing a model based on electronic patient record (EPR) data. The model outperformed MEWS (the Modified Early Warning Score, a previous EWS detailed in Appendix A), as shown by improved sensitivity (51.6% vs. 42.2%), specificity (94.3% vs. 91.3%), and earlier warning of resuscitation and death events than clinical practice (15.9 hours vs. 5.7 hours) [19].

We have identified four potential areas for improvement of the efficacy of EWS, as illustrated in Figure 1.3. These are considered below.

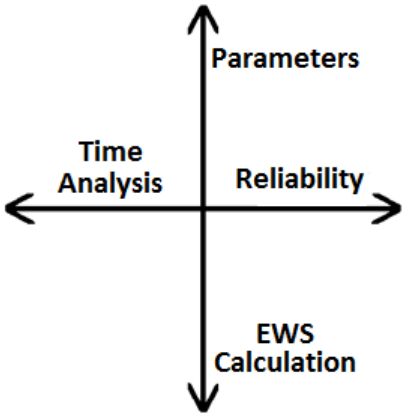

FIGURE 1.3: Possible improvements to EWS

Physiological Parameters

Physiological state is the out-working of the highly complex set of interconnected systems which make up the human body. It is not possible to measure the physiological state of a patient in anywhere near its entirety. The 7 inputs to the NEWS are believed to be the optimal compromise between obtaining sufficient information to describe physiological state precisely, whilst minimising the resources required.

DeVita *et al.* concluded that the performance of EWSs might be improved by including additional variables such as *"patient demographics, co-morbid conditions* [*e.g.* [46]], *changes in patient behavior and functional capacity, ... biochemistry and haematology results"* [20] (as described in Table 1.2). Previously, the resources required to take these into consideration prohibited their inclusion. However, the introduction of electronic medical records in general wards has now made it possible to include additional physiological values such as these in an automated EWS [19, 47, 48]. This might (i) provide a more precise description of physiological state, and (ii) provide earlier warning of deterioration since the additional variables may change earlier than current variables in the deterioration process [49].

The following categories of parameters could potentially be incorporated into EWSs of the future:

TABLE 1.2: Laboratory Test Variables

Variable Type	**Explanation**
Haematology	A complete blood count is obtained by assessment of the constituents of a blood sample, excluding the plasma. The following levels are assessed [50, 51]: haemoglobin (oxygen-carrying protein), red blood cell count (blood cells which contain haemoglobin; count is synonymous with concentration), haematocrit (volume of blood occupied by red blood cells), red blood cell indices (mean cell volume, mean cell haemoglobin, mean cell haemoglobin concentration, red cell distribution width), platelet count, white blood cell count (immune system cells, including a breakdown for the different types of white blood cell: neutrophils, lymphocytes, monocytes, eosinophils, basophils).
Biochemistry	Biochemistry results are obtained by analysing blood plasma. Electrolyte (ions in solution which should be maintained at the right levels such as Na and K), creatinine and urea levels (which both indicate kidney function) can be obtained. Liver function tests report levels of bilirubin and albumin. Coagulation tests indicate the clotting function of the blood.

- *Variability*

  An individual in a healthy physiological state exhibits maintenance of homoeostasis (maintenance of internal equilibrium) which is manifested as slight variability in physiological values over time with a tendency towards a central value. HRV is one specific example. Both decreased and increased variability have been suggested to be indicative of perturbation from health to disease states (see a comprehensive review by Seely *et al.* [52]), and therefore offer potential for early detection of deteriorations [53]. Changes in variability have been associated with infection [54], sepsis [55], severity of illness and organ failure [56]. We hope to investigate this phenomenon by analysing physiological data captured at a much higher frequency than the underlying physiological mechanisms.

- *Categorical parameters*

  'Administration of supplemental oxygen' is the only categorical parameter used in NEWS. However, additional categorical parameters, such as 'heart rhythm' may be indicative of deteriorations. For instance, AF is a common complication of cardiac surgery (with an incidence of approximately 25% [57, 58]), which represents a significant change in physiological state. AF can be detected from ECG signals [59].

- *Contextualisation*

  It may be useful to contextualise parameters according to categorical parameters. For

instance, a HR of 131 bpm in a regular rhythm is very different to a HR of 131 bpm in AF. Similarly, an SpO2 of 97 % on room air is very different to an SpO2 of 97 % whilst receiving four litres of oxygen per minute. This may improve the performance of threshold scoring.

The current inputs to NEWS, particularly HR, SBP and RR, can be influenced by almost all bodily organs. This is advantageous because they will usually become abnormal during the course of a progressing deterioration, regardless of its origin. However, because of their systemic nature they do not typically become abnormal until the deterioration has progressed substantially. Therefore, it may be helpful to either: (i) incorporate parameters which are influenced more strongly by individual organs, or (ii) fuse these systemic parameters in various configurations so that the fused parameters are strongly affected by individual organs [60]. We will investigate each improvement by (i) testing the performance of indices of cardiac function when monitoring the recovery of the heart to an insult, and (ii) creating organ-specific indices of function from systemic parameters.

In addition to enlarging the range of possible physiological inputs, the precision of measurement techniques can be improved. Whilst a range of methods exist for measuring RR (11 are listed in [61]), they have poor precision and are unsuitable for intermittent observations. Consequently, RR is currently estimated by counting chest movements (corresponding to breaths) over approximately 30 s. This is laborious (if done properly, it takes up approximately 1% of nurses' time). For instance, Lovett *et al.* found that the 95% limits of agreement between criterion standard measurements and (i) nurses' measurements, and (ii) impedance plethysmography electronic measurements [1] to be (i) -8.6 to 9.5 bpm, and (ii) -9.9 to 7.5 bpm [61]. Given that the mean RR of hospital patients is approximately 21 bpm [19], these are unacceptable. To address these concerns, we have tested the precision of algorithms which use the ECG and PPG signals to estimate RR. The use of PPG signals is particularly relevant, since these signals are routinely measured when taking observations.

Reliability

There are two consequences to recording an imprecise EWS: (i) an imprecise assessment of clinical risk resulting in compromised patient safety, and (ii) an imprecise record of the patient's

[1] The method routinely used in bedside monitors, which detects breaths by measuring the changes in transthoracic impedance plethysmography using low voltage, high frequency currents.

historical physiology, making clinical review difficult. Therefore, the input of a 'reliability' parameter alongside each physiological parameter could improve the performance of EWS.

There are 3 potential sources of imprecision when measuring a patient's EWS:

1. *Artefactual physiological measurement*
   This is well known in the ICU setting, where patients are continuously monitored, resulting in imprecise measurements due to artefact, subsequent false alarms and staff becoming insensitive to alarms [62, 63]. However, the incidence of imprecise measurements due to artefact on general wards is not well reported. Signal quality indices (SQIs, indicating the quality of the signal from which each automatically estimated physiological parameter is derived) have been used to reject parameters derived from artefactual signal. SQIs can only be used with SBP, SpO2 and HR parameters, since only these are derived from continuous signals [64]. Over 80 such algorithms have been designed for the ICU setting [65]. However, they have been criticised for only being suitable for particular equipment or a particular clinical setting. Therefore, we have developed SQIs which we believe are not susceptible to such shortcomings [66].

2. *Erroneous transfer of physiological measurement to recording medium*
   Imprecise transcription of individual parameters has been criticised as a source of error. For instance, in a small study, Prytherch *et al.* found that 6.7% of physiological parameters were erroneously transcribed to paper charts [67].

3. *Erroneous calculation of EWS from recorded physiological values*
   The precision of manual EWS calculation has been widely criticised [22]. For instance, Smith *et al.* found that in 22% of manual calculations of EWS were incorrect, meaning that 24% of patients whose *"observations should have reached the trigger value did not"* [68].

The latter two sources of error have potential to be eliminated with the introduction of recently developed observation monitors which transmit parameters directly to an EPR an calculate an EWS [69] (such as the IntelliVue MP5SC as part of the IntelliVue Guardian System, Philips Medical Systems, Boeblingen, Germany, and the Connex Vital Signs Monitor 6000, Welch Allyn, Skaneateles Falls, NY, USA). We have trialled both systems, and found that they are not yet ready for clinical use [70].

EWS Calculation

The calculation methodology used in EWS has been criticised for:

1. Not being "scientifically derived", but being based on expert opinion [39].
   This has been addressed by determining thresholds from large physiological databases [23, 32, 71].

2. Being based on threshold scoring [39].
   This is due to threshold alarms having a notoriously low positive predictive value of clinical significance in the ICU setting, such as 3% [35] [72], 5.5% [73], 5.9% [74] and 10.6% [75].
   This has been addressed by Tarassenko *et al.* , who have used the following novelty detection methods [76] to calculate an EWS:

   - **Normalise parameters**
     Each of d physiological parameters, x, is normalised using Equation (1.1) using a normalised value x_n [77]:
     $$x_n = \frac{x - \mu}{\sigma} \tag{1.1}$$
     where μ and σ are the mean and standard deviation of x.
   - **Define probability of observing this set of parameters**
     The probability of observing a set of parameters, $\boldsymbol{x}$, based on n training data, is given by a non-parametric Parzen windows estimate [78]:
     $$p(\boldsymbol{x}) = \frac{1}{nh} \sum_{j=1}^{n} K(\frac{\boldsymbol{x} - \boldsymbol{X_j}}{h}) \tag{1.2}$$
     where X_1, X_2, ..., X_n are independently identically distributed random variables; K is a Kernel function, and h is a smoothing parameter [77].
   - **Approximate training data**
     Since n is often very large, the number of training points is reduced whilst maintaining the approximate distribution using a k-means clustering algorithm [79, 80]. Typically the data is reduced to $N = 400$ [81] or 500 [82] components.
   - **Apply a Kernel function** A Gaussian Kernel function, of dimension d, is commonly used, based on the stability of longitudinal data [77]:
     $$K_x = \frac{1}{(2\pi)^{d/2}} \exp(\frac{x^2}{2}) \tag{1.3}$$

Substituting into Equation (1.2):

$$p(\boldsymbol{x}) = \frac{1}{n(2\pi)^{d/2}\sigma^d} \sum_{i=1}^{N} K(\frac{|\boldsymbol{x} - \boldsymbol{X_i}|^2}{2h^2}) \tag{1.4}$$

where σ^2 is the variance of the Kernel.

- **Estimate the variance of the Kernel** The variance of the Kernel is estimated using the method proposed in [83], in which the 10 nearest neighbours NNs are determined for each component in $\boldsymbol{X}$ [84]:

$$\text{distance, } \Delta_i = \frac{1}{10} \sum_{min} \|\boldsymbol{x_i} - \boldsymbol{x_j}\| \tag{1.5}$$

  σ is then the average Δ over all N points.

- **Calculate the novelty score** The novelty score, or 'Patient Status Index' [82], which decreases with increased probability, is [79]:

$$z(\boldsymbol{x}) = -\ln p(\boldsymbol{x}) \tag{1.6}$$

  This novelty score can be compared to a threshold value to determine whether a particular set of values is abnormal. An adjustment may be required in the tails of the distribution where is more sparse, which can be applied using Extreme Value Theory [85].

Tarassenko *et al.* fused $d = 5$ parameters: HR, $(SBP+DBP)/2$, RR, SpO2, and temp [86] using this technique to produce an EWS (shown for two parameters in Figure 1.4). This methodology has improved EWS performance dramatically, achieving a positive predictive value of 95% [35, 87]. Since this technique has been shown to work well clinically, it is not a priority to compare it to other techniques (which are described in [88])

Time Analysis

Time analysis of physiology has been proposed in the ICU setting [89], but this is impractical for NEWS since it is currently calculated by hand. In contrast, clinicians often review previous physiology to determine the clinical risk of a patient exhibiting abnormal physiology. Given the recent possibility of automated analysis of EPR data, it has been suggested that EWSs should

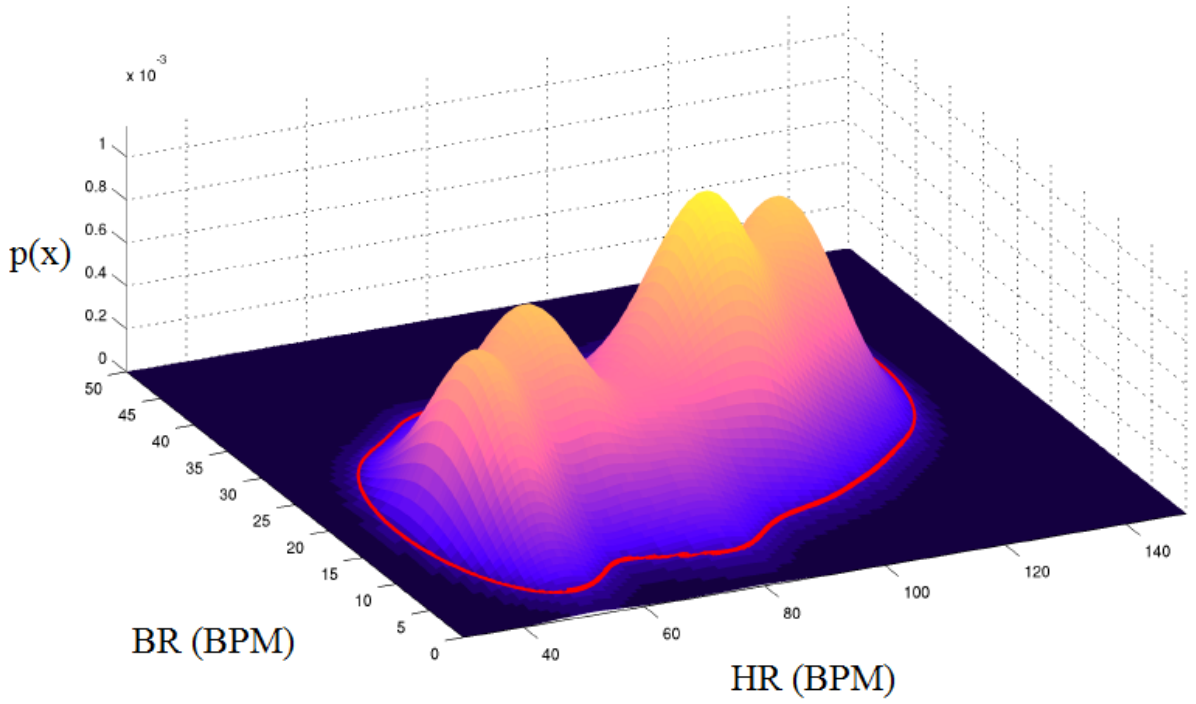

FIGURE 1.4: Probability Density Function (PDF, $p(x)$) for fusion of two parameters, with a threshold of abnormality shown by the red line. [79]

also make use of time series analysis [39, 90, 91]. We believe that clinical review of vital signs performs two functions, which could be beneficial to EWSs:

1. *Time analysis gives an indication of a patient's stable physiological state.*

   In order to determine whether abnormal physiology indicates instability, the patient's stable physiology can be used for comparison. Since patients are often in hospital for a significant time prior to deterioration [92], it is likely that their physiology will have been previously assessed during a time of stability. Therefore, a 'baseline' measurement of stable physiology can often be obtained by review of a patient's physiology.

2. *Time analysis indicates the rate of change of physiology.*

   A knowledge of the rate of change of physiology can be used to estimate the probability of deterioration [93].

We will focus on improving EWSs by incorporating time analysis since this is routinely performed by clinicians when they remain unsure about the clinical risk despite EW scoring. Furthermore, very little research has been conducted into its automation outside of the ICU setting.

Specifically, we have modelled the physiological trajectories of inpatients to investigate the utility of this approach.

1.3 Physiological Trajectories

The word *"trajectory"* is frequently used to describe the progression of an inpatient's illness [94, 95]. It has been used mostly to describe many facets of a patient's progression:

> "the physiological unfolding of a patient's disease, ... the total organization of work done over that course, plus the impact on those involved with that work and its organization." [94]

However, our definition is narrower: *the physiological state of an individual as a function of time*, as illustrated in Figure 1.5.

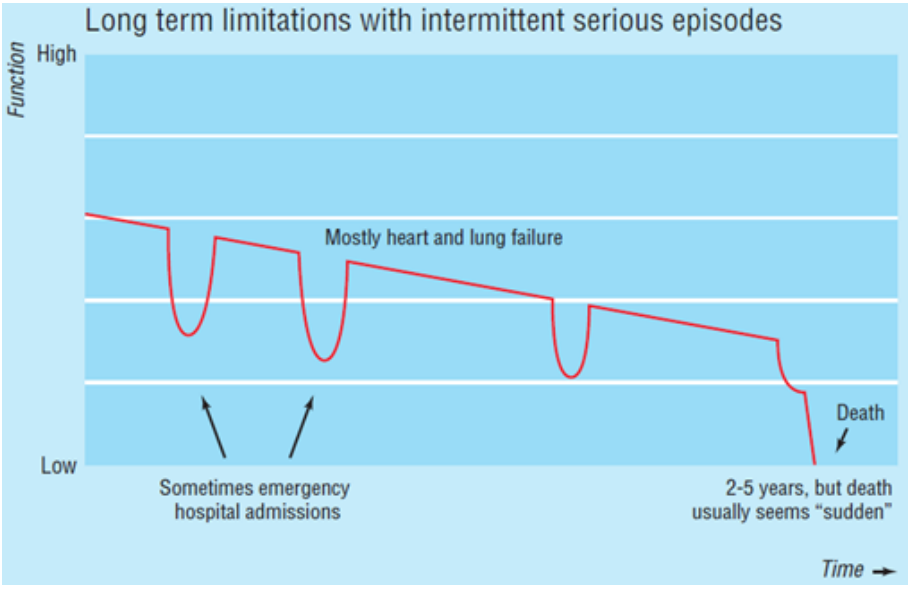

FIGURE 1.5: A typical physiological trajectory of a cancer patient [96].

In the next sections we overview the clinical contexts in which physiological trajectories have been measured, and the mathematical techniques used.

1.3.1 Clinical Contexts

Previous analysis of physiological trajectories has largely focused on cerebral function rather than systemic physiology. Areas of research include:

- **Side-effects of radiation therapy** Levels of fatigue and anxiety have been studied in both patients and caregivers during and following radiotherapy treatment, in which three classes of trajectories have been identified [97]. This has informed hypotheses for the mechanisms underlying morning and evening fatigue [98]. Identification of predictor variables of increased fatigue has facilitated appropriate resource allocation [99, 100] and more accurate assessment of symptoms [101].

- **Postoperative pain** Studies of postoperative pain trajectories highlighted the importance of responding to the rate of resolution (a predictor), as well as level of pain, to reduce the likelihood of chronic postoperative pain [102, 103].

- **Depression** Classes of depression trajectories have been identified in psychiatric inpatients to allow recovery progress to be assessed [104]. Predictor variables of depression during bereavement for a family member have been identified for appropriate resource allocation [105].

- **Child growth** The impact of feeding on child growth trajectories has been studied to make recommendations on the length of time to continue breast feeding [106].

- **Cognitive recovery from traumatic brain injury** Predictor variables of cognitive recovery trajectories after traumatic brain injury have been identified, allowing rehabilitation progress to be evaluated on a patient-specific level [107–109].

- **Predicting cerebral oedema** Durward et al. found that persistently low glucose-corrected serum sodium levels may provide early warning of the onset of cerebral oedema (fluid accumulation in the brain) in patients with diabetic ketoacidosis [110].

- **Recovery of independence after stroke** Trajectories of levels of independence after stroke have been studied, allowing variables which affect initial severity and rate of recovery to be identified [111].

1.3.2 Mathematical Techniques

Linear Regression

The simplest approach used to model patient trajectories is linear regression. The measurement y of individual i on occasion j is modelled as [112]:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \epsilon_{ij} \tag{1.7}$$

Here, the independent variable is time, t, the errors, ϵ, and β are constant coefficients. The order of the underlying function can be increased to a polynomial. This allows the trend to be modelled as a more complex shape, such as a quadratic:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \epsilon_{ij} \tag{1.8}$$

This technique is limited since it assumes: (i) errors are independently distributed, which is not appropriate for longitudinal data; and, (ii) all individuals share the same underlying trajectory. Therefore, it is unsuitable for prediction of deteriorations [112].

Multilevel modelling

Multilevel modelling is an extension of linear regression which addresses these two limitations. It allows analysis of the shapes of trajectories (within-subjects variability), and identification of predictors which discriminate between classes of trajectories (between-subjects variability). Predictors may include baseline characteristics (such as age) and time-varying covariates (such as drug dosage). A basic multilevel model (also known as hierarchical linear model) *"is partitioned into the within-subjects (or Level 1) model"* [112],

$$y_{ij} = b_{0i} + b_{1i} t_{ij} + \epsilon_{ij} \tag{1.9}$$

"and the between-subjects (or Level 2) model",

$$b_{0i} = \beta_0 + \upsilon_{0i}$$
$$b_{1i} = \beta_1 + \upsilon_{1i}$$

Where υ are the random deviations of an individual's trajectory from the population mean.

This is more appropriate for longitudinal data as the errors can now be considered independent, since they have had the *"influence due to individuals removed from them"* [112]. The model order can be increased to a polynomial, and time-varying covariates can be included as additional terms.

Fractional Polynomials

Fractional Polynomials relax the assumption of linearity inherent to linear regression and multilevel modelling [113]. Instead, time-varying parameters can be raised to a restricted set of exponents, M, as suggested in [114, 115]:

$$M = \{\text{-3; -2; -1; -0.5; 0; 0.5; 1; 2; 3}\}$$

These exponents encompass many common non-linear transformations, such as the reciprocal, logarithm ($M = 0$), and square root [116]. This gives three benefits: (i) parsimony (it is not computationally expensive to select optimal exponents from such a restricted set), (ii) a wide range of curve shapes, and (iii) *"the ability to approximate asymptotes"*, which is very important when considering physiological trajectories of recovery [115].

Latent Growth Curve Modelling

Latent Growth Curve Modelling is equivalent to Multilevel Modelling, but is expressed in the structural equation modelling (SEM) framework. Equation (1.9), which described a 2-level multilevel model, can be re-written using SEM notation as [117]:

$$y_{ij} = \lambda_{0j}\ \text{intercept}_i + \lambda_{1j}\ \text{slope}_i + \epsilon_{ij} \tag{1.10}$$

$$\text{intercept}_i = \beta_0 + \upsilon_{0i}$$
$$\text{slope}_i = \beta_1 + \upsilon_{1i}$$

Here λ_{0j} are the factor loadings for the intercept factor, and λ_{1j} are the factor loadings for the slope factor, which both vary with time [117]. Trajectory parameters (such as slope) can be easily incorporate as predictors of outcome [117], giving them utility beyond Mulitlevel Models. This methodology assumes that patients are members of observed populations - *i.e.* predictors such as age must be postulated [118].

Growth Mixture Modelling

Growth Mixture Modelling extends Latent Growth Curve Modelling by introducing latent (hidden) variables to identify unspecified subpopulations. In doing so, the probability that a patient

belongs to a particular population can be calculated from their trajectory. One such model is illustrated in Figure 1.6:

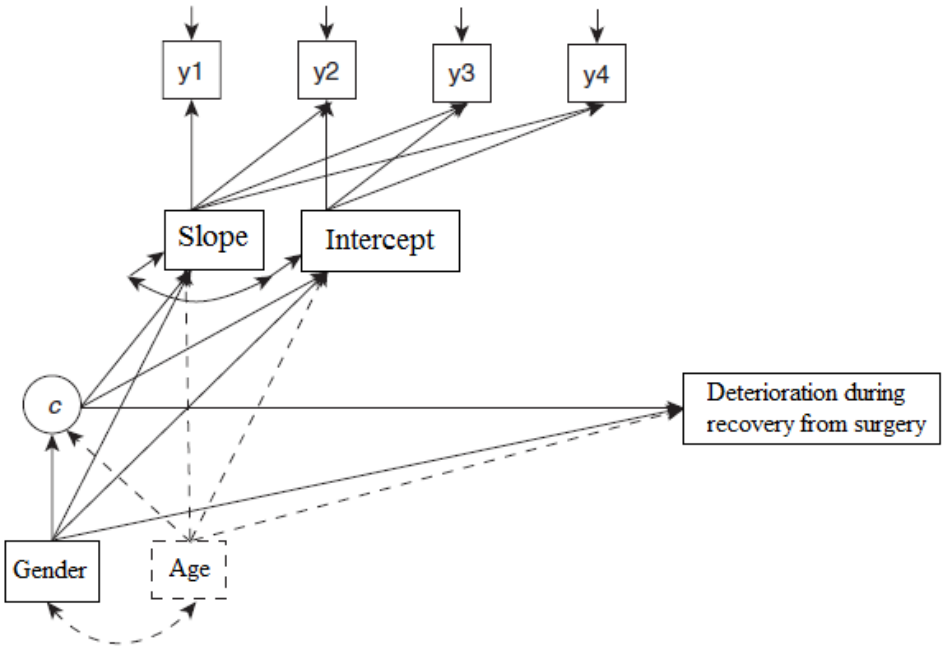

FIGURE 1.6: A Growth Mixture Model with two covariates (gender and age), slope and intercept parameters describing the physiological trajectory monitored at time points y1 to y4, and a dichotomous outcome variable of whether or not the patient deteriorates after surgery. Time-varying covariates are omitted for simplicity. (Adapted from [119])

A multinomial logistic regression model can now be used to estimate the probability the class membership (c) of an observed physiological trajectory is one of K classes, given (for instance) one covariate (x_i) [119],

$$P(c_i = k|x_i) = \frac{e^{\gamma_0 k + \gamma_1 k x_i}}{\sum_{s=1}^{K} e^{\gamma_0 s + \gamma_1 s x_i}} \tag{1.11}$$

where γ_0 and γ_1 are the logit intercept and slope of the relevant class [118].

The probability of deterioration can now be estimated by [119]

$$P(\text{deterioration } |c_i = k, x_i) = \frac{1}{1 + e^{\tau_k - \kappa_k x_i}} \tag{1.12}$$

where τ_k is a class-varying threshold and κ_k is a class-varying slope for x [119].[2]

[2]Further details are given in [111].

Gaussian Process Regression

Gaussian process regression has recently been suggested for characterising physiological trajectories [120, 121]. Gaussian processes are a generalisation of the Gaussian distribution from a vector space to a functional space [122], which are fully specified *"by a mean and covariance function"* [122]. The hyperparameters can be learnt from previous input data, and made to vary with time, making patient-specific predictions possible. However, the covariance function must be specified. In keeping with previous work, the squared exponential will be used (Equation (1.13), where x are input values, σ_0 is the maximum allowable variance, and λ is the time length scale) [77]:

$$K(x_i, x_j) = \sigma_0^2 \exp(-\frac{1}{2}\frac{|x_i - x_j|^2}{\lambda}) \tag{1.13}$$

Gaussian processes are advantageous to the previous methods, since they allow prediction of missing (or future) values of physiological state. A posterior probability distribution over the missing values can be inferred [77], where the mean is the predicted value, and the variance informs confidence limits in this prediction. Therefore, the likelihood of observing an incoming physiological state can be evaluated, which can be transformed to a likelihood of deterioration.

1.4 Monitoring Physiological Trajectories for Earlier Detection of Deteriorations

We propose three methods for detection of deteriorations using physiological trajectories:

Trajectory Class

If a patient's mean trajectory belongs to a class of trajectories which culminates in deterioration, it would indicate oncoming deterioration. There are two stages to implementing this. Firstly, physiological trajectories of deteriorating and non-deteriorating patients will be analysed to identify differences. Secondly, variables (both fixed and time-varying) which contribute to these differences will be identified so that the calculation of physiological state can be optimised.

Dynamic Behaviour

Dynamic changes in physiology can be assessed:

1. *In the absence of significant dynamic external factors*
   Abnormal variance in a patient's trajectory may indicate oncoming deterioration (since this illustrates abnormal variability in physiology) [123]. This could be assessed over a range of timescales, since physiological signals can oscillate on the order of seconds to a whole day [46].

2. *In response to dynamic external factors*
   For instance, the rate of return of heart rate to baseline after exercise has been shown to be predictive of mortality [124, 125]. Helpfully, techniques exist to detect a change in posture [126, 127], which would precede and follow exercise, from physiological signals.

Patient-specific normality

EWSs have been developed using population-wide data. Several authors have suggested that the calculation should be tailored to the specific patient and disease process [62]. We will incorporate patient-specific prediction by quantifying their deviation from their predicted trajectory. We will use two inputs to predict their trajectory:

1. *Admission variables*
   Admission variables may well predict recovery trajectory. Many admission scores have been developed to predict mortality, such as the Charlson score, a *"weighted index of co-morbidity"* which indicates the 10-year risk of mortality of a medical patient based on their co-morbidities (disorders in addition to their primary diagnosis) [128]; and the EuroSCORE, for prediction of early mortality in cardiac patients [129]. Since physiology varies with demographics such as age [130, 131], race and sex, it may be useful to calculate a model of normality accordingly.

2. *Previous physiology*
   A predicted trajectory should also adapt to acute changes in physiology, requiring previous physiological inputs. For instance, it has been suggested that alarms should adapt to the patient over time [132–134].

1.5 Transfer Report Overview

This report gives an overview of the completed and planned work for each of the four steps required to determine whether deteriorations of inpatients could be detected earlier by monitoring their physiological trajectories (Figure 1.7).

FIGURE 1.7: Proposed stages of work.

Chapter 2 describes constructing a database of monitored physiology, and initial calculation and monitoring of physiological trajectories. Chapters 3 and 4 describe methods for estimating RR and markers of cardiac function, and initial evaluations thereof, respectively. Chapter 5 outlines our conclusions and proposed future work.

Chapter 2

Constructing a Physiological Database

2.1 Introduction

A database of longitudinal physiological measurements and accompanying annotations of deteriorations was required on which to test the hypothesis. Many databases are publicly available (for instance, 7 are listed in [135], and many others are available on PhysioNet [136]). However, those which contain longitudinal data are mainly in the ICU setting. In the ICU physiology is artificially normalised by pharmacology and interventions, making it a difficult setting in which to test the hypothesis. Therefore, we chose to record our own data. This gave the added advantage that the *'errors in collection, measurement, transmission, transcription and storage of data'* which are present in these databases would be known to us, and we could attempt to mitigate them [64]. This chapter details the construction of this physiological database.

2.2 Methodology

2.2.1 Patients

We chose to monitor patients for the remainder of their hospital stay after cardiac surgery since this facilitated construction of a physiological database, as detailed in Table 2.1:

TABLE 2.1: Criteria and justification for monitoring cardiac surgery patients.

Criterion	Justification
Non-deteriorating patients should exhibit broadly the same physiological trajectory	Patients recovering from the same type of major surgery have received the same physiological insult. Following surgery patients typically regain independence and control over their bodily functions [137]. Therefore, a post-surgical population is expected to follow a recovery trajectory from a (reasonably) uniform initial physiological state.
Physiology should be continuously monitored to provide trajectories at the highest possible sampling frequency.	On a general ward, only cardiac patients are continuously monitored to give early warning and diagnosis of potentially fatal arrhythmias and cardiac arrests.
Laboratory tests should be regularly performed to incorporate these parameters.	Laboratory tests are typically performed daily in the cardiac surgery population.
A reasonable proportion of patients should deteriorate	Cardiac surgery has lower complication (approximately 10-20% [138, 139]) and mortality rates (approximately 3% [140]) than other types of surgery, such as vascular surgery. However, since wireless continuous monitoring is already in use on post-cardiac surgery wards, we chose to study this population.

Patients due for elective or emergency cardiac surgery at St Thomas' Hospital, London, were approached for consent between November 2012 and December 2013 as approved by the Bloomsbury London Ethics Committee (National Clinical Trial 01549717, known as LISTEN). Patients usually follow the pathway illustrated in Figure 2.1 after cardiac surgery at St Thomas'.

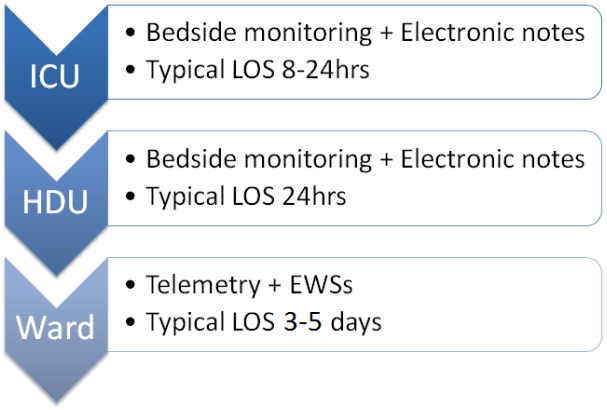

FIGURE 2.1: Recovery pathway after cardiac surgery at St Thomas' Hospital: ward, monitoring procedures, and typical length of stay (LOS).

2.2.2 Data Collection

We used routine monitoring equipment to collect continuous data since novel technologies are often unreliable [141]. Bedside monitors were used (IntelliVue MP70, Philips Medical Systems, Boeblingen, Germany) in critical care (Overnight Intensive Recovery (OIR), and HDU). When transferred to a general ward, patients were asked to wear a telemetry (wireless) monitor (IntelliVue M4841A, Philips Medical Systems) which monitored both ECG (lead II) and PPG, giving continuous coverage of these signals throughout recovery. These allow continuous estimation of three NEWS parameters: HR and SpO2 (routinely), and RR (retrospectively, see Chapter 3).

Several methodologies for acquisition of continuous data from monitors were considered, as illustrated by Figure 2.2. We used BedMaster (Excel Medical Electronics, Jupiter, FL, USA),

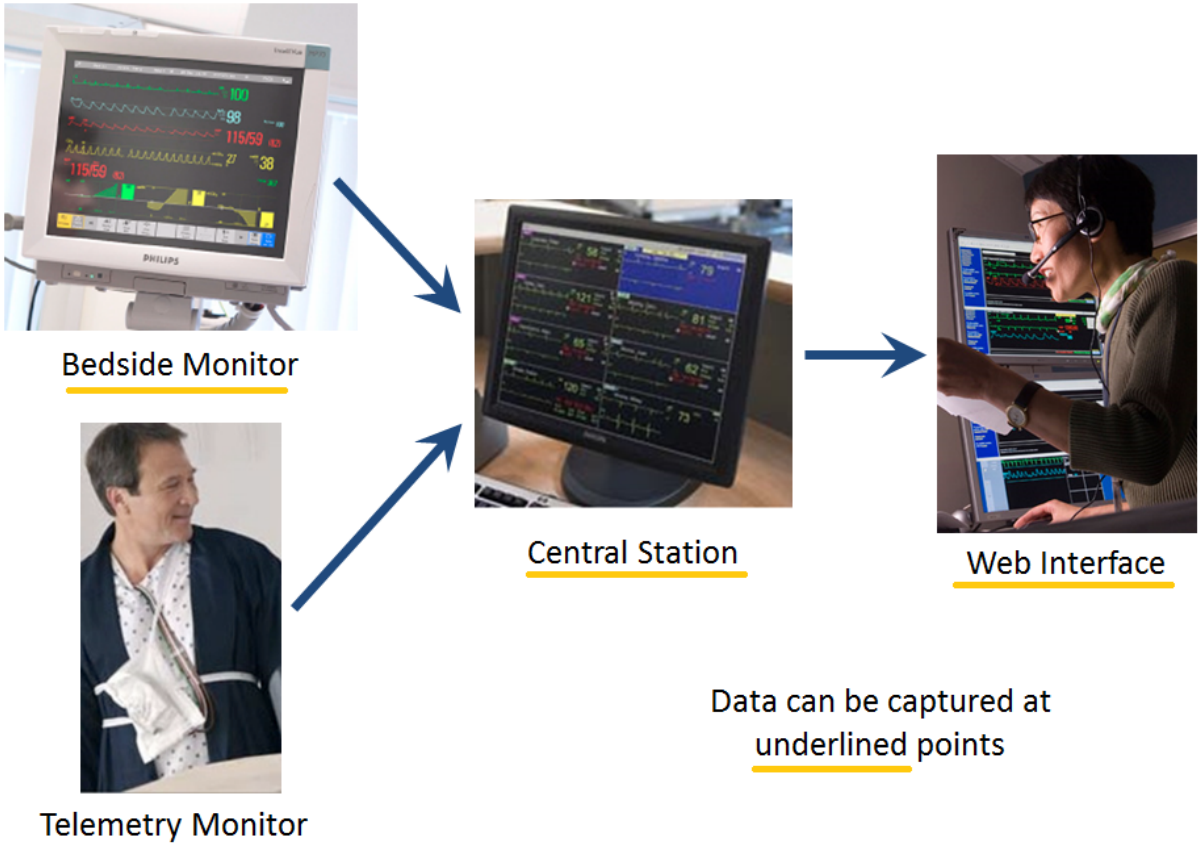

FIGURE 2.2: Methodologies for recording from Philips monitors: Data can be captured from Philips monitors at three points (with citations for different systems which capture data from these points): (i) the bedside monitor ([142–146], not applicable for telemetry monitors); (ii) the central station [135]; (iii) the web interface, where BedMaster acquires data [147, 148]. Images from [149]

since it requires no infrastructural changes. This allowed all signals to be recorded from the

monitors, giving invasive BP and thoracic electrical impedance signals whilst in critical care. Details of the data formatting methodology are given in Appendix C.

Haematology and biochemistry values were queried from the hospital's EPR. A researcher visited the patients each day, and recorded any clinical events (as defined by [150]). EWS observation data was independently transcribed from paper charts by two researchers, with any discrepancies resolved by the second transcriber.

2.2.3 Data Processing

Correction of timestamps

Data acquired using BedMaster is sometimes incorrectly timestamped, as illustrated in Figure 2.3. The simultaneous data could either be discarded (leaving gaps), or an algorithm developed

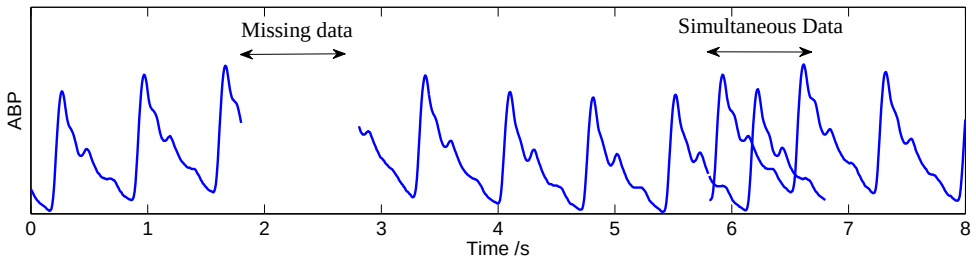

FIGURE 2.3: An erroneously timestamped ABP waveform (from LISTEN001). Errors result in simultaneous data at some timestamps, and missing data at others. No attempt was made to determine the source of such errors. Instead, rules were implemented to either remove or correct erroneous data.

to correct the timestamps. The cost of discarding simultaneous numerics was expected to be minimal, since numerics are measured so often (1 Hz). In contrast, signal analysis often requires a segment of uninterrupted data, and therefore a single gap (*e.g.* one second) prevents analysis of a whole segment (*e.g.* one minute). Since many errors were due to delayed sections of data, the proposed correction method was:

1. Find gaps of 1 s duration followed within 60 s 1 s of simultaneous data.
2. Check whether the data between the gap and simultaneous data (the intervening data) are continuous. If not, take no action.

3. If so, shift the intervening data by one second. [1]

A waveform corrected using this method is shown in Figure 2.4.

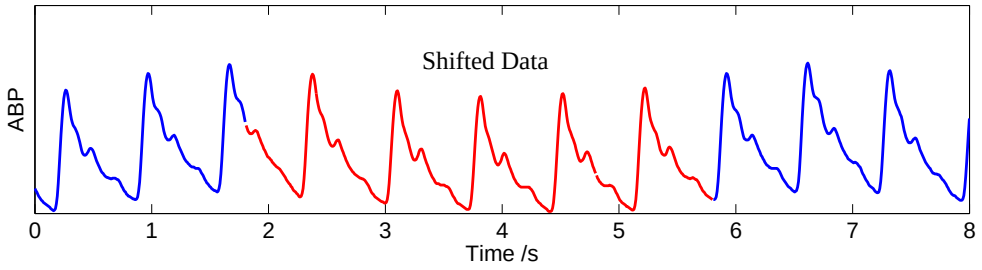

FIGURE 2.4: The waveform shown in Figure 2.3, after the timestamps have been corrected by shifting a segment of the data by one second.

Beat Detection

Beats were detected from ECG signals by identifying R-peaks (indicating ventricular contraction) using the algorithm described in [151, 152] (as shown in Figure 2.5). [2] Beats were detected

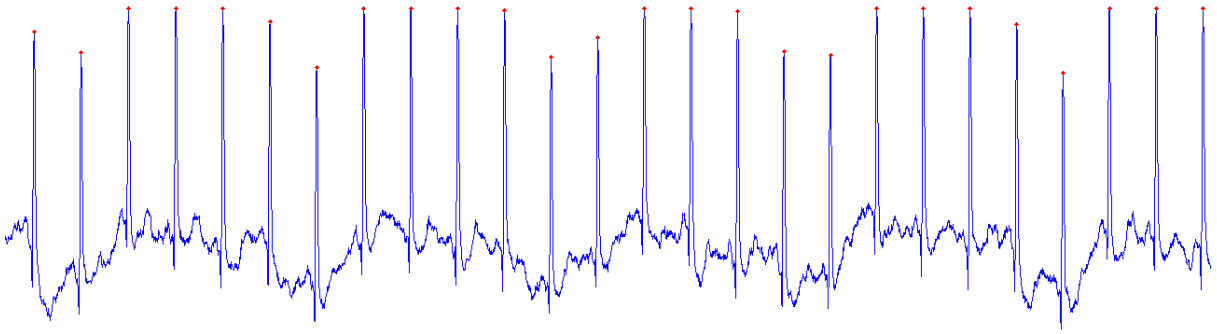

FIGURE 2.5: R-peaks detected from an ECG signal (shown in red) using the widely-accepted Pan, Hamilton and Tompkins algorithm.

from PPG signals by identifying pulses (indicating arterial pulse waves) using a bespoke peak detector. [3]

[1] Since the order of the data points is retained from the BedMaster data, it was assumed that the values at the first repeated timestamp occurred physiologically prior to the second repeated timestamp.

[2] This algorithm was originally written by Gari Clifford, and adapted by Mark Ebden, Thomas Brennan, David Clifton (all University of Oxford) and Peter Charlton.

[3] This algorithm was written by David Clifton, and modified by Iain Strachan (OBS Medical, Abingdon). A point was classified as a peak if (i) it satisfied a 3-point peak detection algorithm, and (ii) the PPG subsequently decayed beyond an adaptive threshold without encountering a higher 3-point peak.

Signal Quality Assessment

Following beat detection, ECG and PPG signals were quality assessed using an algorithm developed by Orphanidou *et al.* [66]. Firstly, derived beat-to-beat intervals are assessed for physiological plausibility. Secondly, template matching is used to quantify the correlation between an averaged beat's morphology and that of each indvidual beat. If the correlation coefficient is below an empirical threshold value, then the signal quality is deemed to be poor, otherwise it is good (as shown in Figure 2.6). Unlike other methods, this can be applied to individual signals, and is supposed to be independent of monitoring equipment or clinical setting.

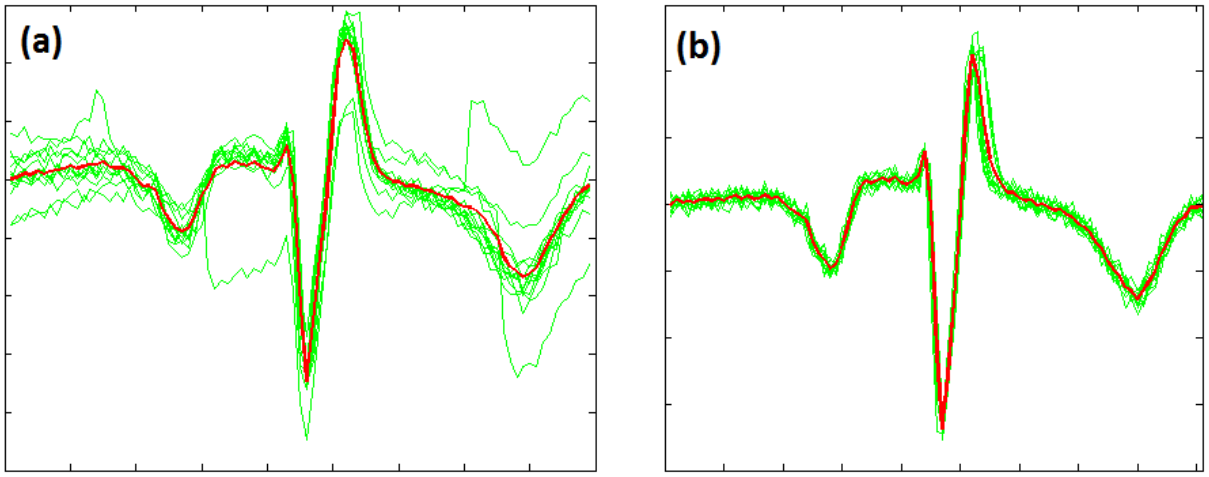

FIGURE 2.6: SQI calculation by template matching of beats for 10 s ECG segments: (a) overlaid beats giving a correlation coefficient of 0.89, indicating poor quality (template in red); (b) a correlation coefficient of 0.97, indicating good quality.

Physiological Trajectories

Gaussian processes were used to plot some preliminary physiological trajectories, since they allow confidence intervals to be constructed. One dimensional kernel density estimates were constructed based on a patient's data from their entire stay. The squared exponential covariance function and Gaussian likelihood function were used. Physiological state was simply calculated as sum of the likelihoods of the HR and SpO2 values.

2.3 Preliminary Results

2.3.1 Patients

227 patients participated in the study, of which 226 have been discharged. One patient withdrew consent, so the database contains data from 225 patients. Demographic characteristics are given in Table 2.2.[4] Observed clinical events are listed in Table 2.3.[5] The mortality rate was 1.5%.

TABLE 2.2: Demographic Characteristics of 225 patients

Characteristic	
Age, y (median ± IQR)	68 ± 16
Gender, male (No. (%))	166 (74)
Ethnicity (No. (%))	
White	209 (93)
Mixed	2 (1)
Asian	6 (3)
Black	7 (3)
Other	1 (0)
Surgery Type (No. (%))	
Bypass	108 (48)
Valve	145 (64)
Other	33 (15)

2.3.2 Data Collection

97 patients were withdrawn from the study, consisting of 70 patient requests to stop wearing telemetry, 19 leaving the study pathway, 7 for clinical reasons, and 1 withdrawal of consent. 200 patients had the opportunity to wear telemetry, of which 130 wore it until discharge. The median length of stay was 7 days (see Figure 2.7). Figure 2.8 summarises the ECG and PPG data collected from one example subject. Transcription of observation data has been completed for 196 patients. The details of these 3998 observation sets are given in Table 2.4. The proportion

[4] A patient may have more than one type of surgery.

[5] Those events listed as 'Other' are largely administration of plasma and platelets, but confirmation of these is ongoing.

Table 2.3: Recorded Clinical Events

Event	Frequency
Transfusion <8 units	262
Other	199
Unplanned cardiac pacing	96
Atrial fibrillation requiring treatment	51
Acute Kidney Injury	45
Sepsis (except pneumonia)	41
NIV/CPAP	39
Unplanned return to surgery	19
Stroke/TIA	10
Insertion of pleural drain on ward	10
Ventricular tachycardia	9
Altered mental state	9
Asystole	7
Commencement of inotropes	7
Diarrhoea	5
Arrhythmia not specified elsewhere	5
Reintubation	4
Ventricular fibrillation	4
Deep wound infection	4
Pneumonia or lung infiltrate	3
Died	3
Seizure	2
Cardiac failure	1
Bleeding	1
Pneumothorax	1
Coma	1
Bowel obstruction	1
DNAR order	1
Acute MI	0
DVT	0
Patient injury	0
Internal organ damage	0
Sudden death	0
Transfusion reaction	0
Pulmonary embolus	0
Limb ischaemia	0
Insertion of pericardial drain on ward	0
Insertion of other drain on ward	0

of time for which each physiological signal was recorded in each setting is given in Figure 2.9. ECG and PPG data was recorded for only 71 and 31% of the time spent on the general ward prior to withdrawal.

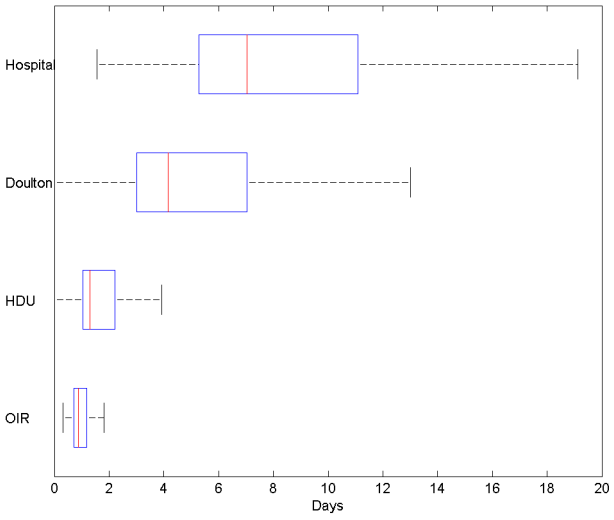

FIGURE 2.7: Box and whisker plots for the length of stay in hospital (post-surgery), and on each ward in the typical pathway. Whiskers include data within 1.5 IQR of the 25th and 75th quartiles.

TABLE 2.4: Parameters recorded in 3998 observation sets

Parameter	**Frequency (%)**
Temperature	3692 (92)
Heart Rate	3789 (95)
Systolic BP	3926 (98)
Diastolic BP	3925 (98)
Mean BP	210 (5)
Respiration Rate	3795 (95)
O2 Saturation Level	3894 (97)
O2 Therapy	3851 (96)
PAR score	3700 (93)

Data could not always be recorded whilst patients were being monitored, for reasons including: (i) the patient was off the ward on at least 335 occasions, preventing data capture; (ii) computers (central stations and the acquisition server) failed on at least 24 occasions, and (iii) the acquisition software malfunctioned on at least 27 occasions.

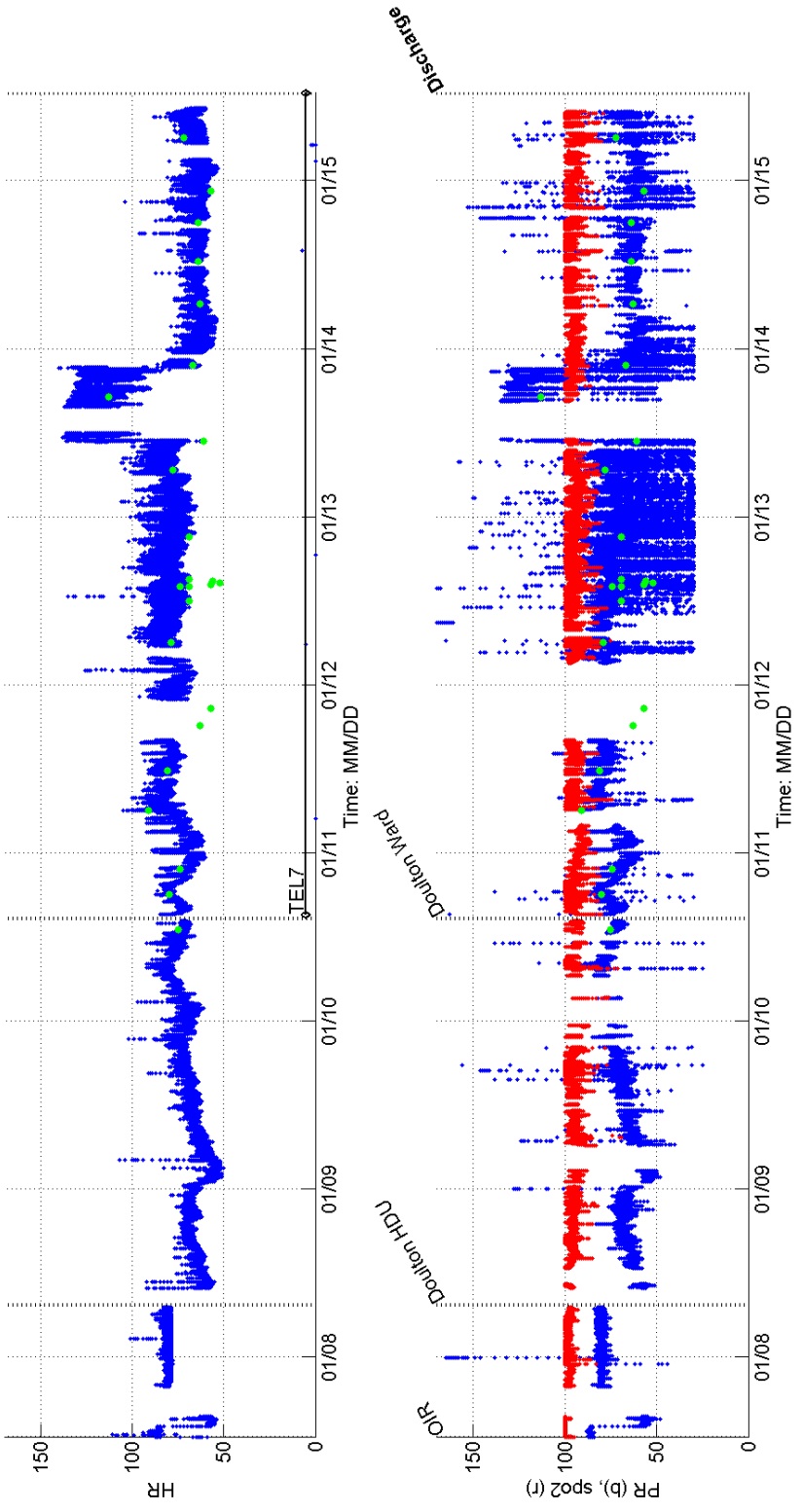

FIGURE 2.8: Continuous data collected from LISTEN009, showing the HR numerics given by the monitoring equipment, estimated from the ECG (top plot) and PPG (lower plot). SpO2 numerics are shown in red on the lower plot. The HRs recorded in ward observations are shown in green.

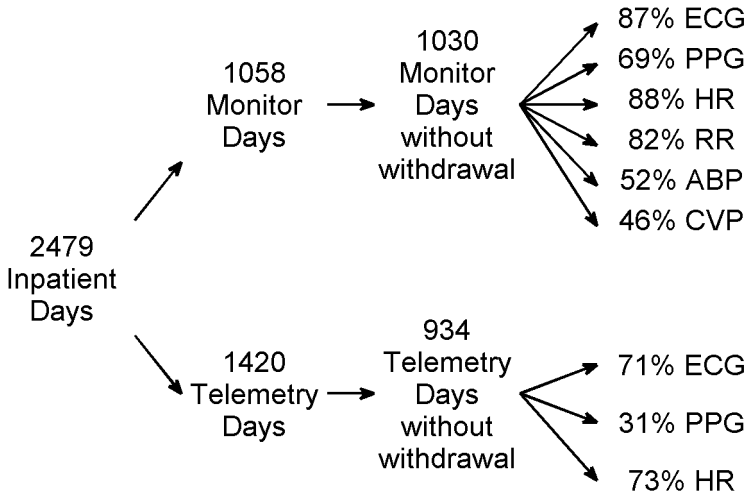

FIGURE 2.9: The proportion of time for which each signal was recorded during LISTEN.

2.3.3 Data Processing

The timestamp correction algorithm was tested on data from the first 25 LISTEN patients (Table 2.5). There were a mean of 28.3 gaps of 1 s per patient-hour in hospital in the continuous data. Gaps were present in data acquired from both bedside and telemetry monitors. Beat detection was performed on ECG and PPG signals, facilitating the use of SQIs. The benefit of using the SQIs is illustrated by Figure 2.10.

TABLE 2.5: Performance of the timestamp-correction algorithm

Median ± IQR	Percentage available			Percentage of possible segments reclaimed by algorithm
	Before processing	After elimination of simultaneous data	After correction algorithm	
Data points	86.5 ± 13.2	85.8 ± 13.4	87.2 ± 13.5	
Complete 10 s segments	72.9 ± 17.4	72.2 ± 17.1	80.7 ± 22.1	69.6 ± 62.9
Complete 30 s segments	70.8 ± 7.2	70.5 ± 7.2	79.0 ± 12.5	54.4 ± 43.6
Complete 60 s segments	62.8 ± 10.9	62.8 ± 10.9	75.5 ± 18.4	44.2 ± 46.8

Two exemplary physiological trajectories are shown in Figures 2.11 and 2.12:

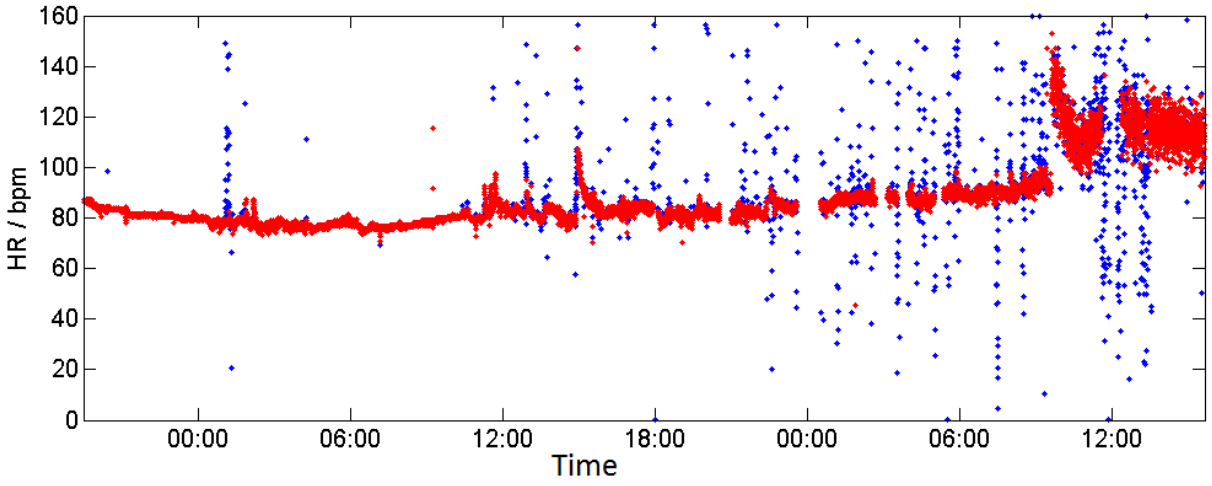

FIGURE 2.10: HR values determined from poor (blue) and good (red) quality PPG signal segments in the critical care setting (LISTEN002). Those derived from good quality segments are more stable. Note that the SQI still functioned during atrial fibrillation (AF) in the last six hours.

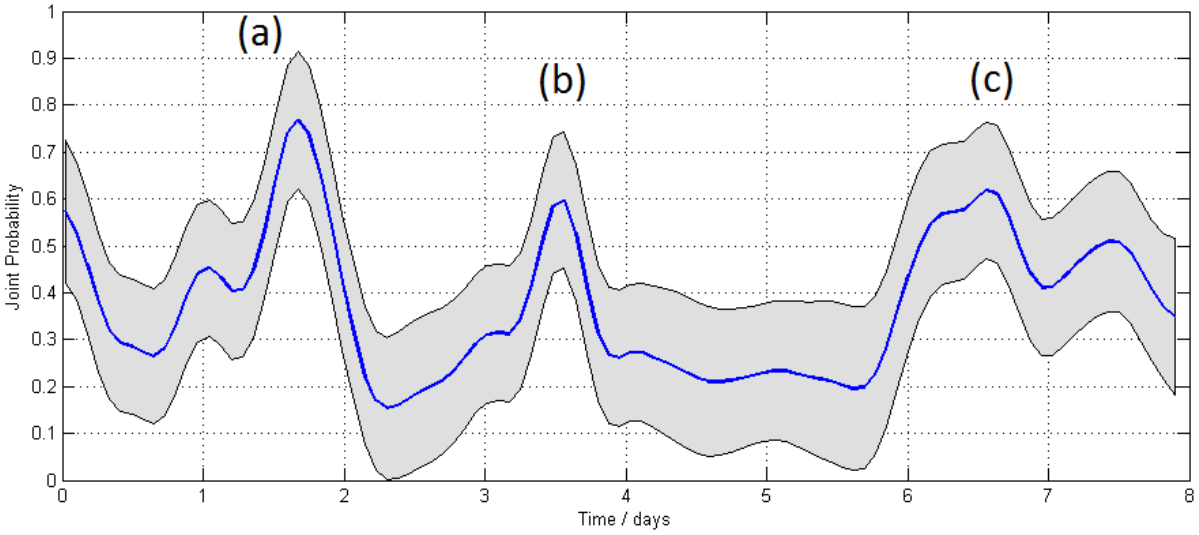

FIGURE 2.11: An example physiological trajectory of the mean of the likelihoods of continuous SpO2 and HR values. The peaks correspond to extreme physiology: (a) desaturation to SpO2 = 88% at 1.7 days; (b) desaturation to SpO2 = 87% at 3.5 days; (c) atrial fibrillation at 5.9 days. Taken from LISTEN009

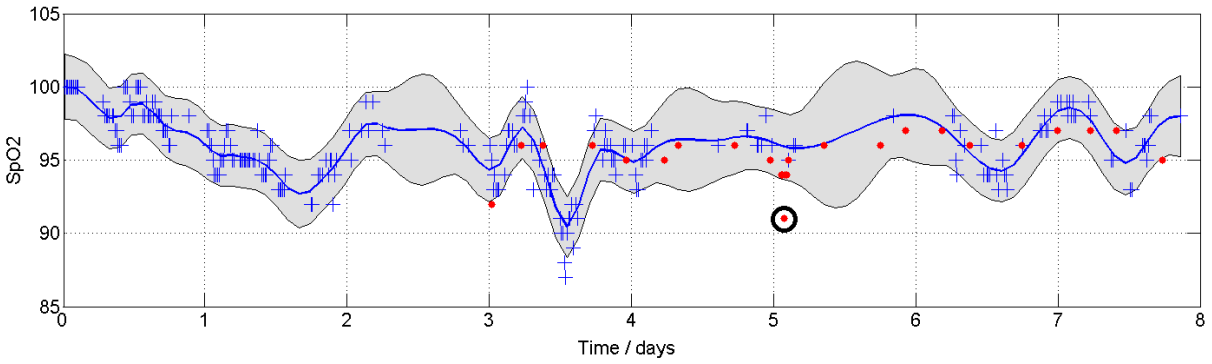

FIGURE 2.12: Detection of erroneous observation data: A trajectory of continuous SpO2 values (+) has been plotted (mean in blue and 95% confidence intervals). Manual observation data recorded on the general ward is plotted in red. The circled measurement at 5.1 days is likely to be erroneous. Taken from LISTEN009

2.4 Discussion and Conclusions

We have collected all routine physiological data from a large cohort of patients post-cardiac surgery. To our knowledge, this is the first study in which three NEWS parameters have been recorded continuously from ambulatory patients until discharge. The physiological data is complemented by expert annotation of clinical events. There were sufficient deteriorations for testing algorithms for detection of deteriorations.

The telemetry monitor was not well tolerated, as shown by only 65% of patients opting to wear it until the end of their stay, and PPG data being acquired for 31% of time on the general ward. However, this coverage will still provide a much higher frequency of the three continuous parameters than available from ward observations alone, allowing trajectories to be calculated more precisely.

Imprecise timestamps substantially reduced the proportion of time for which signals could be analysed. Our timestamp correction algorithm was highly effective, as shown by a median of 69.6% of possible 10 s segments being reclaimed by the algorithm. Since the data was timestamped after transmission across a network, we tentatively suggest that this was due to transmission delays across network switches. SQIs have been implemented to ensure that imprecise data is eliminated.

We have presented two initial physiological trajectories, demonstrating the utility of Gaussian processes. Figure 2.12 shows that as well as being useful for detecting deteriorations, trajectories could be used to detect erroneously recorded observation data. This would require a

multidimensional kernel density estimate, since it is very difficult to distinguish between an acute deterioration and a transcription error with only a single parameter. This should be implemented, along with automated optimisation of hyperparameters.

In conclusion, we believe that this database provides the highest coverage of physiology measured in a post-cardiac surgery cohort. Therefore, it is a valuable resource for testing our hypothesis.

Chapter 3

Monitoring Respiratory Rate

3.1 Introduction

Many studies have found RR to be highly predictive of deteriorations [14, 19, 26, 29, 153, 154] (as described in Appendix B). However, it is inaccurately and poorly measured [61, 155–157]. Techniques exist for estimating RR from the ECG and PPG signals (collected in LISTEN study). However, there is little evidence for their precision when used with ambulatory inpatients. If a sufficiently precise algorithm can be validated or developed, then RR could be a third continuous input for modelling physiological trajectories. This chapter describes work on evaluating the precision of these techniques in healthy volunteers.

3.1.1 Physiological basis

The ECG is influenced by respiration due to: (i) changing orientation of the electrical axis of the heart during respiration; (ii) changing thoracic impedance; and, (iii) respiratory sinus arrhythmia (RSA, variation in heart rate with respiration, [158]). The first two mechanisms result in varying QRS-amplitudes (amplitude modulation, AM) and baseline wander (BW). The latter modulates R-R intervals (frequency modulation, FM). We have previously described the physiological mechanisms by which respiration influences the PPG [159], although these are not fully understood [160]. It is influenced by changes in venous return and stroke volume due to changing intrathoracic pressure during respiration, changes in tissue volume due to varying arterial pressure, and RSA. These result in AM, respiratory-induced intensity variation (RIIV,

equivalent to BW) and FM respectively. Addison *et al.* illustrated these influences on the PPG, as shown in Figure 3.1.

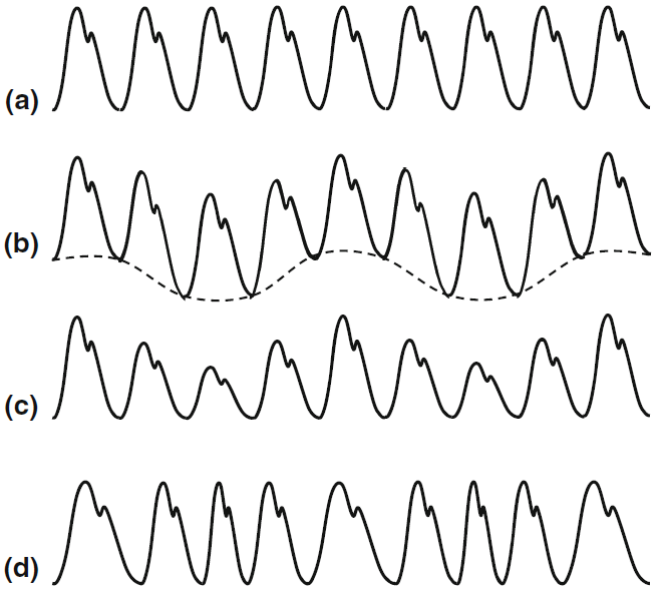

FIGURE 3.1: Respiratory modulation of the PPG: During two respiratory cycles: (a) no modulation, (b) baseline wander (BW), (c) amplitude modulation (AM), (d) frequency modulation (FM).

3.1.2 RR algorithms

Techniques for estimating RR from the ECG have been comprehensively reviewed in [161]. Many techniques require signals from more than one lead. However, those which require only one lead use techniques which are also applicable to the PPG, since the modulations of the signals are equivalent (AM, FM and RIIV / BW). Techniques for use with the PPG (and, therefore, a single-lead ECG) have been reviewed in [162–164]. An up-to date overview of the techniques is presented here since this is still a rapidly developing field.

RR algorithms consist of four components, as described in Figure 3.2. The prior art for each is described below.

Signal Quality Indices

The SQIs detailed in Section 2.2.3 are designed to determine whether a segment of signal is of sufficient quality to reliably quantify HR. The first part of these algorithms, which rejects

FIGURE 3.2: The four components of an RR algorithm: (i) **SQI:** An SQI is used to reject any poor quality data, since it is unlikely to result in a precise RR measurement; (ii) **Extract Time Series:** A time series of respiratory modulation is extracted by either digital filtering or beat-by-beat feature measurement; (iii) **Sample Evenly:** Some algorithms require time series to be evenly sampled; (iv) **Estimate RR:** The respiratory frequency is estimated from a time series; (v) **Fuse Estimates:** Estimates obtained using either different features, or different signals, are fused to give one RR estimate.

data for which instantaneous HR derived using peak detection is implausible, has been used to eliminate poor quality signal prior to RR estimation [165]. However, the thresholds have not been designed specifically for RR estimation. Very few methods for specifically estimating the quality of a signal for RR estimation have been proposed. Two methods have been proposed based on the relative dominance of the dominant peak in the frequency domain after pre-processing [166, 167]. This area requires further research.

Time series extraction

Either the raw signal can be used as time series, or beat-to-beat features can be extracted as a time series. The steps for the latter are: (i) detect beats, (ii) measure a feature present on each beat (such as QRS amplitude), and (iii) create a time series consisting of one measurement per beat. Several beat detectors have been used (such as those described in Section 2.2.3). The precision of a final RR estimate is highly dependent on the detector. However, since most detectors perform well with good quality signal, SQIs reduce the dependency of the algorithms on the detectors. A variety of feature measurements have been proposed, as illustrated in Figure 3.4. Beat-by-beat measurement of any feature gives a time series of measurements (*e.g.* Figure 3.3).

Sample evenly

Time series extracted using feature detection will be unevenly sampled (since beats occur irregularly). If the technique used to estimate RR from the time series operates in the frequency domain, then the time series will need to be re-sampled at a fixed frequency (typically 2 or 4 Hz). This can be achieved by holding each value until the next measurement, and sampling this

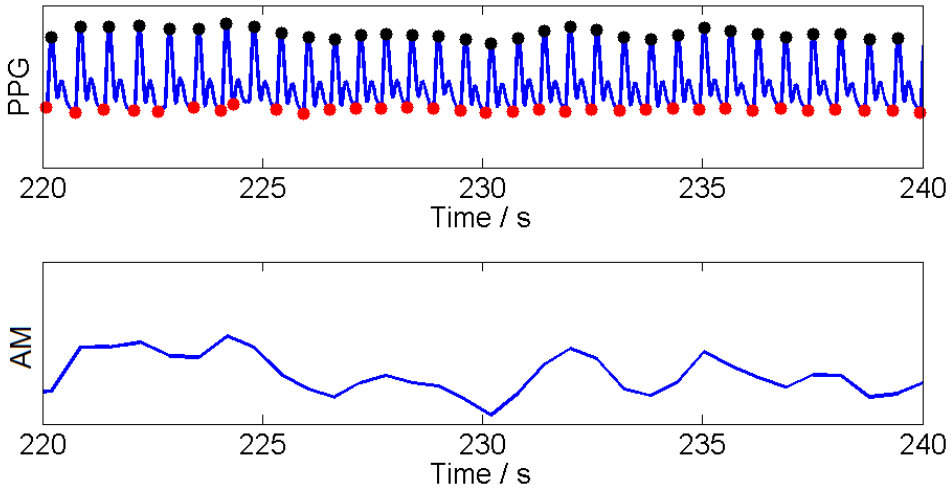

FIGURE 3.3: Time series extraction using feature measurements from a PPG signal: In the upper plot, peaks (black) and troughs (red) are detected after beat detection. The lower plot shows a time series of amplitude measurements (absolute peak amplitudes), where ideally each cycle would represent a breath. Taken from VORTAL027.

continuous signal. Berger *et al.* presented a more sophisticated approach, whereby the value can vary within a beat, providing a smoother re-sampled signal [171]. This has been widely used.

Estimate RR from time series

Lindberg *et al.* were the first to propose that RR could be monitored using the PPG, in 1992 [172]. Despite achieving a sensitivity and PPV of over 99% for detection of individual breaths in young male volunteers, new techniques are still being proposed over 20 years later. A search was made for all techniques used in at least two publications. These are illustrated in Figure 3.5, and detailed below.

The 'digital filters' technique is still in use [173], despite being the first documented method. A regularly sampled time series is required. This is either band-pass filtered [172, 174] or low-pass filtered [175] to isolate frequencies of interest. Several cut-off frequencies have been suggested, including fixed and adapting frequencies, representing the plausible frequency range of RR (which varies according to patient population) and other periodic influences (such as HR). These are given in Table 3.1. If it is assumed that after filtering, the dominant frequency in the signal is respiratory, then individual breaths can be detected using either 'peak-detection' or 'zero-crossings' methods [168], as illustrated in Figure 3.6. This is analysis of BW.

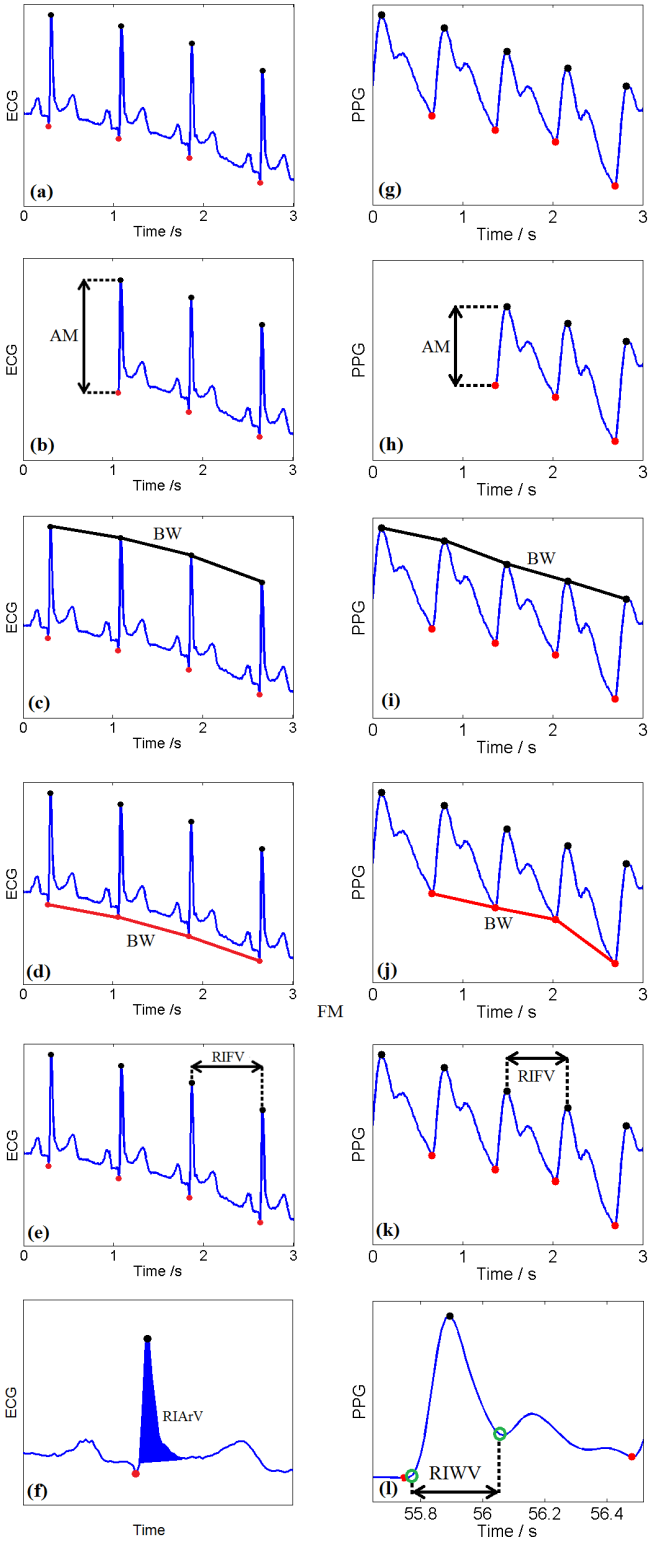

FIGURE 3.4: Features for RR estimation: Beats are detected, after which troughs (red) and peaks (black) can be identified, (a) and (g). AM is measured here as peak-to-trough amplitudes, (b) and (h), but many approaches can be adopted. Two are shown for BW measurement (c, d, i, j) [168]. FM measurement is shown in (e) and (k). Other measurements have been proposed, such as respiratory-induced area variation (f) [169] and respiratory-induced width variation (l) [170].

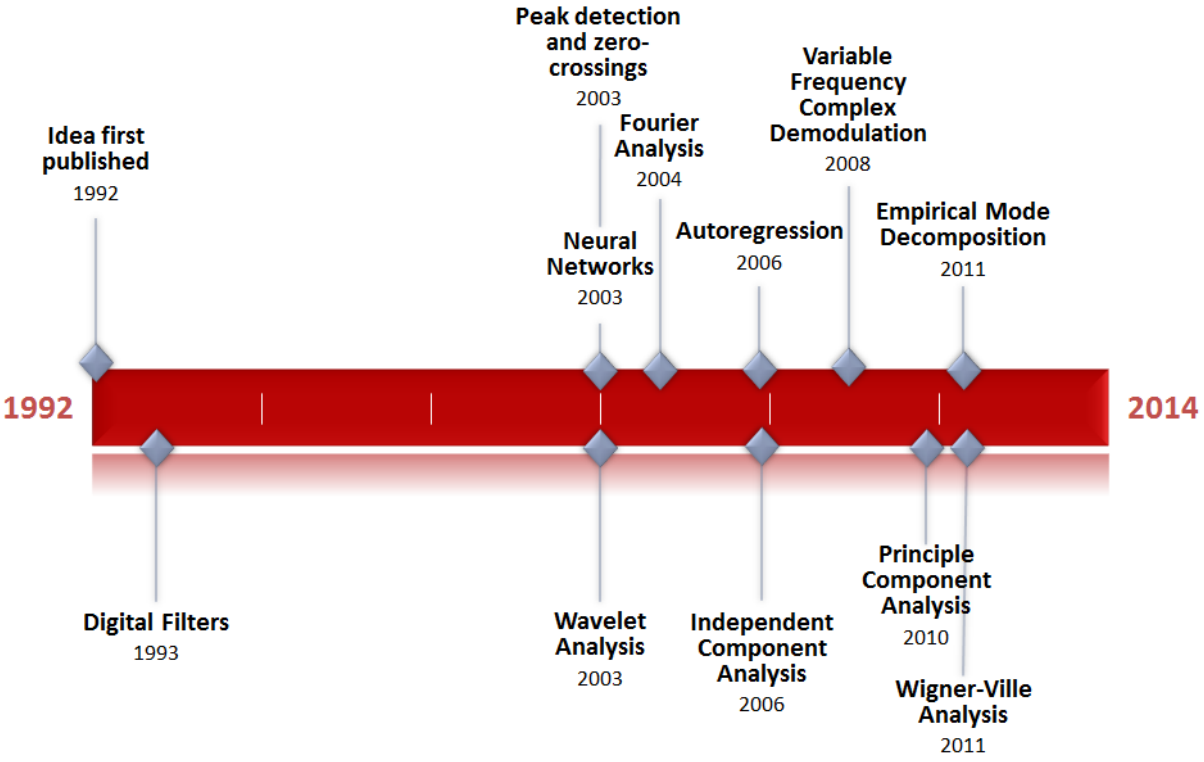

FIGURE 3.5: A timeline showing when each technique for RR estimation from time series was first documented in the PPG literature.

TABLE 3.1: Cut-off frequencies for RR estimation

Lower Frequency (Hz)	**Upper Frequency (Hz)**	textbfCitation
0.1	0.4	[172]
0.13	0.48	[174]
-	0.3, 0.4, 0.55	[175]
-	0.6	[176]
-	HR/2	[177]

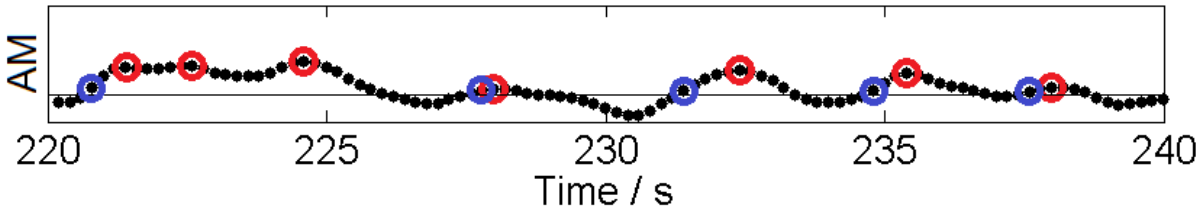

FIGURE 3.6: Peak detection and zero-crossing methods for detection of breaths: the former assumes one 3-point peak per breath (red circles), and the latter assumes that the mean of the signal is crossed once per breath (blue circles), making the methods susceptible to noise, as shown by discrepancies between 220 and 225 s. Taken from VORTAL027

Neural Networks transform a set of inputs to outputs by (i) performing weighted sums of the inputs, and (ii) using an activation function to transform these values to outputs. Johansson *et al.* trialled a neural network, which took as inputs: amplitude (peaks, troughs and peak-trough differences), BW (by bandpass filter) and FM features from the previous five beats [168]. These were fed into a feed-forward neural network with one hidden layer of calculations, to determine whether this segment was more likely to be during inspiration or expiration (using a feed-forward configuration with sigmoid activation functions). They found that using a neural network with five inputs did not, in their healthy subjects, improve performance substantially beyond that of an individual input.

Fourier analysis has been used to extract the respiratory frequency from a segment of regularly-sampled signal. Several time series from the PPG have been used: raw and low-pass filtered signals [178], AM, FM and BW signals [165]. Usually these signals are filtered to isolate respiratory frequencies (if not already), so that when a Fast-Fourier Transform (FFT) is applied, the dominant frequency is the respiratory frequency. This technique cannot perform well when RR is non-stationary across a segment (optimally approximately 30 s in length [165]).

Wavelet analysis was designed to provide greater resolution in both time and frequency than the FFT, reducing the impact of non-stationarity. When implementing wavelet analysis, Addison *et al.* summarised the importance of AM and FM analysis, as well as BW analysis, as illustrated in Figure 3.7. They coined this technique 'Secondary Wavelet Feature Decoupling' [179–183], and it has now been implemented by Covidien Respiratory and Monitoring Solutions [184].

Autoregressive analysis, first proposed in 2006 [185], uses linear regression to find an approximate polynomial function underlying a time series. A detrended and filtered PPG signal can be used [176], or an evenly sampled time series of features [186]. Each point is approximated as a weighted sum of the previous p points, with an error (Equation 3.1) [176]:

$$x(n) = -\sum_{k=1}^{p} a_k x(n-k) + e(n) \tag{3.1}$$

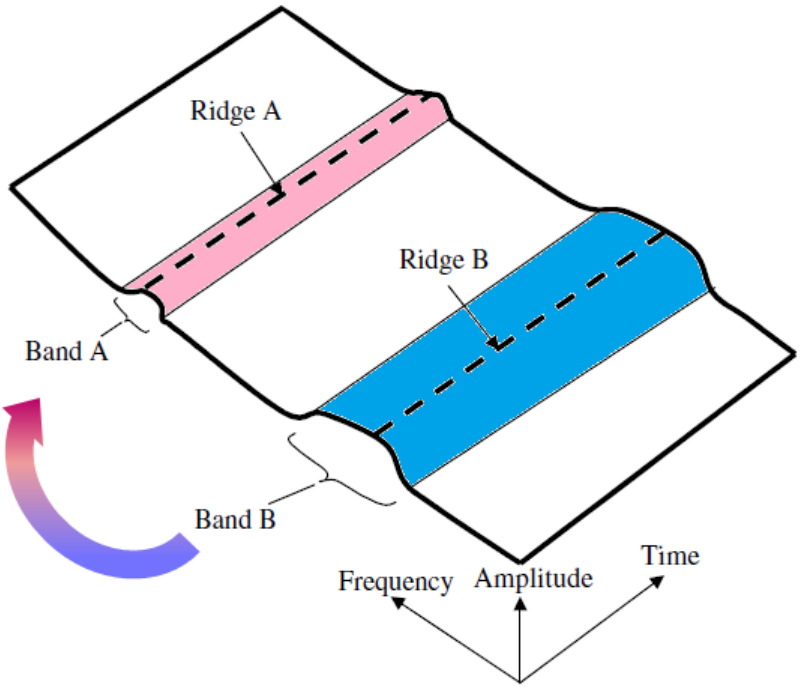

FIGURE 3.7: The rationale for AM and FM analysis in RR estimation: Ridge A represents the cardiac band, and ridge B represents the respiratory band. Ridge B is wider because it also contains influences of Traube-Hering-Mayers rhythms and vasomotion, whereas eidge A consists of only the more powerful HR influence. Therefore, the intuitive extraction of RR from ridge B alone is typically imprecise. However, the respiratory system modulates both the amplitude (AM) and frequency (FM) of ridge A. Hence, AM and FM analysis can be used to estimate RR. Adapted from [180]

Typically the Burg algorithm [176] or Yule-Walker equations are used. This can be considered as *'a system with input $e(n)$, and output $x(n)$'*, with transfer function H [176]:

$$H(z) = \frac{1}{\sum_{k=0}^{p} a_k z^{-k}} \tag{3.2}$$

$$= \frac{z^p}{(z - z_1)(z - z_2)...(z - z_p)} \tag{3.3}$$

The poles of the all-pole transfer function *'define spectral peaks in the power spectrum of the signal, with higher magnitude poles corresponding to higher magnitude peaks.'* [176] The peak with the highest magnitude is selected as the respiratory peak, and a frequency, f, is obtained from its angle in the imaginary plane, θ, using $f = \frac{\theta}{2\pi\Delta T}$, where ΔT is the sampling interval [176]. This magnitude of the pole can be used to assess the quality of the estimate, and for noise rejection. Many suggestions have been made to optimise the choice of model order and peak selection process [187–193].

Independent Component Analysis has been proposed as a method for utilising both wavelengths

of PPG obtained in a pulse oximeter. This is beneficial since the two signals are attenuated differently by arterial and venous blood (infrared is more highly attenuated by arterial blood, whereas the red wavelength contains more of the variation in venous blood volume. Changes in intrathoracic pressure during respiration can have a marked impact on the diameter of the inferior vena cava, modifying the resistance to venous flow from the vasculature. Therefore, it would be helpful to distinguish this component of the PPG signals. This is detailed in [194, 195]. However, since only the infrared wavelength is routinely monitored, this is not discussed further here.

Principle component analysis (using the covariance method) has been proposed for extraction of RR from a band-pass filtered PPG [196–199]. The HR is identified using the singular value ratio of the raw signal. Data is then aligned in a matrix, with each row containing data from one heart beat. The eignvectors corresponding to the three largest eigenvalues of this matrix are used as candidate transformations for a respiratory signal, on which FFT analysis can be performed to determine RR [196].

Other techniques such as Variable Frequency Complex Demodulation ([200–202]), Empirical Mode Decomposition ([203]), and Wigner-Ville Analysis ([204]) have been used. These are largely developments of previous methods, proposing the use of different techniques to estimate the frequency (RR) of a noisy sine-wave (time series).

Fuse Estimates

Different RR estimates can be obtained from: (i) different input signals (*e.g.* PPG and ECG); (ii) different modulations (*e.g.* PPG AM and PPG FM); and (iii) different techniques (*e.g.* PPG AM using Fourier analysis and PPG AM using autoregression). Methods for the first two situations have been proposed:

- *Fuse autoregressive estimates*

  If multiple estimates have been derived using autoregression, then the estimate with the highest corresponding magnitude of pole can be assumed to be the most precise. [205]

- *Arithmetic mean*

  Perhaps the simplest way to fuse estimates is to take the mean of individual estimates. Karlen *et al.* did so, with the proviso that any estimates derived from poor quality signal are not included [165].

- *Neural Network Fusion*

  Neural networks produce one output from several input time series, so are by their nature fusion algorithms. They have been applied to time series derived from the same signal in [168], and to time series from different signals, such as ECG and PPG in [206].

- *Peak-conditioned average*

  When Fourier analysis is used to obtain estimates, their relative precisions can be judged by determining the power contained within a frequency interval either side of the peak. Lazaro *et al.* included any remaining peaks which were at least 75% the power of the previous estimate in an average.

- *Stationarity*

  It is reasonable to assume that an individual's respiratory rate will only change slowly. Therefore, Karlen *et al.* eliminated any estimates which exhibited a standard deviation of ≥ 4 bpm over time [165]. Similarly, Nemati *et al.* assumed that a high quality time series would exhibit a regular breathing pattern, and therefore one spectral peak. They defined a 'purity' function, which measures the dominance of the dominant peak [167].

Given the wide range of RR algorithms for ECG and PPG, yet a lack of translation into clinical practice, we sought to determine their precision in healthy volunteers using both ideal signals (obtained without pre-processing), and routine monitoring signals.

3.2 Methodology

3.2.1 Patients

This study was approved by the London Westminster Ethics Committee (National Clinical Trial 01472133). 18 young (<40 years old) and 12 elderly (>70 years old) healthy volunteers (YHVs and EHVs) were recruited between September 2012 and January 2014. Exclusion criteria included: any co-morbidities affecting the lungs, heart and autonomic nervous system; and, hospitalisation or significant medication within the past 3 months.

3.2.2 Data Collection

Nine continuous signals were acquired throughout the procedure, from three devices:

- *Analogue-to-Digital Converter*

  Analogue (ADC) ECG, defibrillator output ECG (from the bedside monitor), ear and finger PPG, and Nasal air pressure signals were acquired using an analogue-to-digital converter (Power 1401, Cambridge Electronic Design - CED, Cambridge, UK) and Spike2 acquisition software (v.7.09, CED). All were sampled at 2000 Hz except the pressure signal (500 Hz). No filtering was applied, to ensure that all frequency components were preserved.

- *Philips Bedside Monitor*

  ECG, finger PPG (both 125 Hz) and thoracic electrical impedance (62.5 Hz) signals were acquired from a bedside monitor (IntelliVue MP30, Philips Medical Systems) using ixTrend software (v.2.0.0 Express, Ixellence GmbH, Wildau, Germany).

- *Research Pulse Oximeter*

  Finger PPG was acquired using a Nonin 3150 pulse oximeter (Nonin Medical, Inc., Plymouth, MN, USA) using bespoke software [1] since this pulse oximeter has been widely used in prior research [163, 164, 177, 207, 208].

Four autonomic nervous tests were carried out to determine whether a volunteer's autonomic nervous system was functioning as normal (HR and BP response to standing, HR response to a Valsalva Manoeuvre, and HR response to deep breathing, as described in [209]). Signals were then recorded for 10 minutes whilst lying at rest.

3.2.3 Data Processing

The results of autonomic function tests were calculated using beat-to-beat HR derived from the ECG. Any subject which failed more than one test was deemed to have abnormal autonomic function.

ECG and PPG signals recorded at rest were processed for AM, FM and BW algorithms. Beat-to-beat amplitudes and HRs were obtained using R-spikes of the ECG and peaks and troughs of the PPG. These signals were used for time-domain methods. For frequency domain methods, 4 Hz signals were obtained by: (i) resampling beat-to-beat signals at the original sampling frequency using 'sample and hold', (ii) filtering these signals for respiratory frequencies, and (iii) decimating to 4 Hz. BW was estimated using steps (ii) and (iii) on a raw signal. This gave

[1] Designed by Mauricio Villarroel Montoya, Institute of Biomedical Engineering, University of Oxford, UK

5 and 9 respiratory signals derived from the ECG and PPG respectively (shown for the PPG in Figure 3.8):

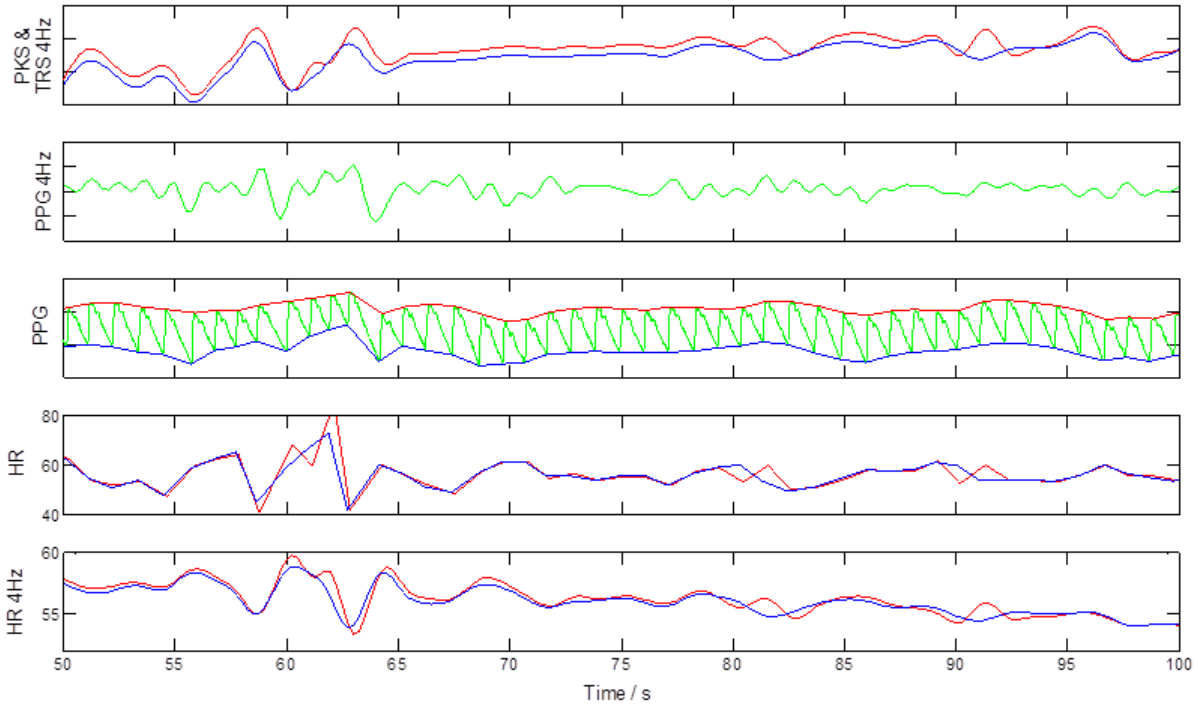

FIGURE 3.8: A finger PPG signal (shown in green in the centre plot), and its nine derived respiratory signals. Signals derived from peaks (PKS) are shown in red, and those from troughs (TRS) in blue. In the top plot, each 4Hz signal has been detrended using constants for ease of comparison. Taken from VORTAL001.

Digital filter, Fourier, and autoregressive analysis were used to estimate RRs from each possible combination of input signal and analysis technique (using 30 s windows). Although an annotating tool has been designed, individual breaths have not yet been annotated. Therefore, the RR given by the bedside monitor (using impedance) was used as a reference.[2] Errors were quantified as root mean square error (RMSE) for each subject, giving an overall mean RMSE for each combination. Subgroup analysis was conducted for young and elderly volunteers.

3.3 Preliminary Results

18 young, and 12 elderly, volunteers have been recruited. All young healthy volunteers (YHVs) passed the autonomic function tests, and 6 elderly volunteers (EHVs) passed. The results are shown for the best three PPG and ECG estimates in Table 3.2:

[2] An impedance signal was not available in two recordings, so a breathing rate calculated using autoregression with the nasal pressure signal was used for these cases.

Table 3.2: Performance of RR algorithms

Signal and technique	Mean RMSE ± SD		
	All	YHV	EHV
PPG (ADC finger), autoregression, BW	5.3 ± 4.5	4.1 ± 1.5	8.7 ± 8.3
PPG (ADC finger), autoregression, AM	5.3 ± 5.0	4.0 ± 1.7	9.1 ± 9.0
PPG (ADC ear), autoregression, AM	5.6 ± 5.2	4.2 ± 1.8	9.8 ± 9.1
ECG (ADC defibrillator), autoregression, BW	5.8 ± 3.8	4.9 ± 1.7	8.5 ± 6.6
ECG (ADC), autoregression, BW	5.9 ± 3.9	5.1 ± 1.8	8.3 ± 6.9
ECG (ADC defibrillator), autoregression, AM	6.0 ± 5.3	4.3 ± 1.9	10.9 ± 8.6

In these preliminary results it appears that the PPG estimates are more precise than the ECG estimates, and that the algorithms are more precise when used with young rather than old volunteers. Estimates derived from raw signals outperformed those from commercially-available equipment. Only the autoregression technique featured in the three most precise algorithms for each of PPG and ECG. Both AM (all derived using peaks) and BW estimates featured.

3.4 Discussion and Conclusions

We have begun to assemble a database of multiple ECG and PPG signals alongside gold standard respiratory signals, for validation of RR algorithms. Preliminary results show that the methodology was justified. Firstly, it was beneficial to use bespoke equipment with an ADC, since estimates derived from these signals outperformed those from commercial equipment. This will allow recommendations to be made regarding the technical specification of monitoring equipment. Secondly, estimates from YHVs appeared to be more precise than those from EHVs, highlighting the impact of age (and possibly reduced autonomic nervous function) on the precision of RR estimates. Finally, despite having a much higher coverage of ECG in LISTEN than PPG, the PPG estimates appeared to be more precise, providing justification for using PPG despite its lower coverage.

The SD of RMSEs was much higher in the EHVs than YHVs, suggesting a much more heterogeneous group. Further analysis of the autonomic function tests may elucidate possible physiological reasons for this.

Three key steps remain. Firstly, these algorithms should be trained on data collected before this study (20 YHVs), since these were initial implementations. Secondly, the autonomic function tests should be re-visited to ensure that the analysis is robust (see Figure 3.9). Finally, further techniques should be implemented. Implementation of other techniques is being carried out in a collaboration with the University of Oxford.

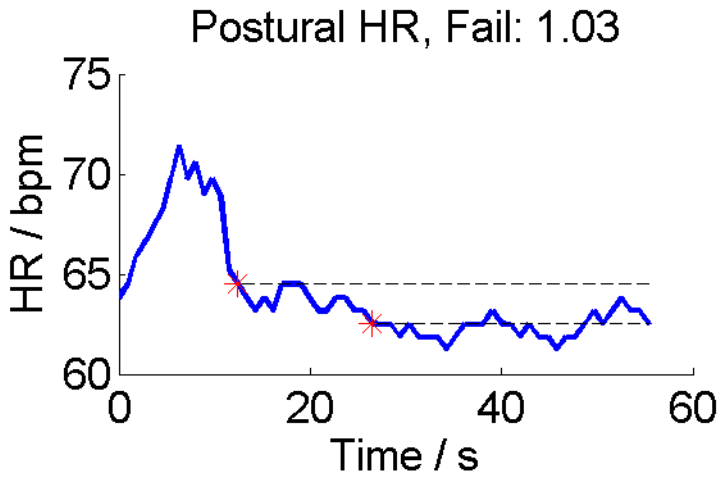

FIGURE 3.9: HR response to standing: the analysis of an autonomic function test. Here, the ratio of 1.03 between the 15th and 30th beat after standing (at time = 0 s) is the recommended measurement. However, if this had been between the 10th and 30th beat, then the subject may well have passed this test. Taken from VORTAL050.

Chapter 4

Monitoring Cardiovascular Function

4.1 Introduction

In 1995, 28% of deteriorations post-cardiac surgery were cardiac [150]. [1] Since the cardiac and vascular systems are often lumped together as the cardiovascular system, it is reasonable to monitor the cardiac and vascular systems to detect these events. In addition, other complications such as infection affect the cardiovascular system. We propose two mechanisms by which cardiovascular function may change after surgery:

1. *Changes in cardiovascular function may precede deteriorations*
   Indices of cardiovascular state are associated with mortality in chronic diseases [210] and may, therefore, be predictive of acute deterioration.

2. *Variability in cardiovascular function immediately after surgery*
   Since cardiac surgery provides a major perturbation to the state of the heart, the early response of the cardiovascular system post-surgery may indicate its eventual resting state (and, therefore, a possible deterioration). This may be measured using the absolute, or variability, in state (both of which are demonstrated in Figure 4.1).

Whilst the cardiovascular system influences the routine NEWS parameters, more specific parameters have been proposed, which can be derived from the continuous signals acquired in LISTEN. In this chapter we outline these parameters, and consider their utility for monitoring physiological trajectories.

[1] This figure is based on incidence of the following complications after CABG: congestive heart failure (the inability of the heart to pump sufficiently), cardiac events and cardiac emergencies.

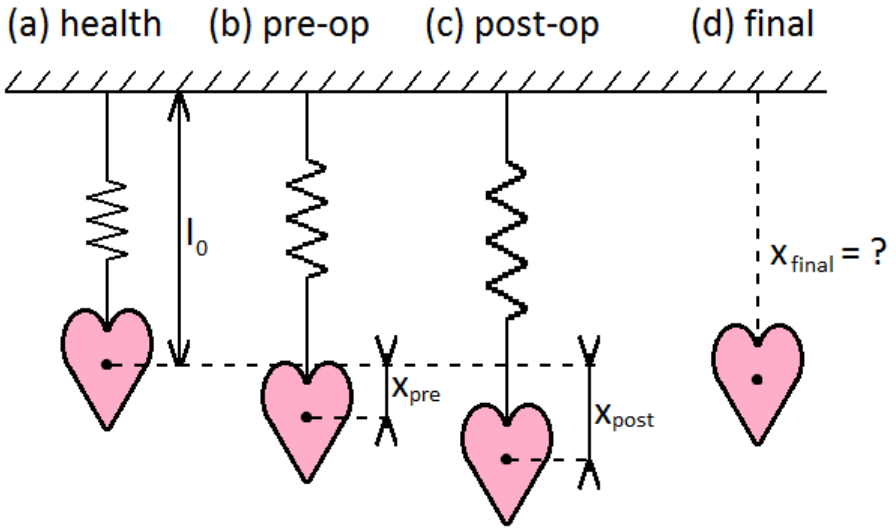

FIGURE 4.1: Perturbation of the heart due to cardiac surgery: The state of the heart, represented by an oscillating spring, (a) during health, (b) immediately pre-operatively, (c) immediately post-operatively, (d) finally after recovery. It is proposed that longitudinal analysis of markers of cardiac function (and their variability) will indicate whether the heart is likely to reach equilibrium at a state of health finally after recovery. Using this analogy, l_0 is the unstretched spring length, and x is the elastic extension due to a force.

4.2 Parameters

Only parameters derived from the ECG and PPG (measure of blood volume [165]) signals could be used to detect deteriorations in LISTEN. The sub-cardiac variability of the PPG reflects autonomic control of the vasculature [211], whereas in the ECG it relates to autonomic control of the heart [211, 212]. Mechanisms underlying Low-frequency, LF (0.04-0.15 Hz), and high-frequency, HF (0.15 0.6 Hz), oscillations are detailed in Table 4.1. These mechanisms show that

TABLE 4.1: Frequency components of PPG and ECG signals.

Signal	Frequency	Mechanisms
PPG	LF	Influenced by sympathetic and parasympathetic, vasomotor activity, with minimal direct vagal influence [213–215].
	HF	Respiratory fluctuations in peripheral blood volume and vagal parasympathetic modulation of the heart rate, alongside modulation of venous return and stroke volume by intrathoracic pressure change.
ECG	LF	Influenced by both sympathetic and parasympathetic modulation, due to baroreflex regulation.
	HF	Vagal parasympathetic modulation of the heart rate due to respiration.

the ECG and PPG contain complementary information about autonomic control of the heart and vasculature. The following cardiovascular parameters derived from ECG or PPG could be indicative of deteriorations:

- *Heart Rate Variability (HRV)*

  HRV has been used as *"a prognostic marker for cardiovascular diseases"* and for *"estimation of cardiac autonomic nervous system activity"* [216]. It has particular application with specific pathologies, such as predicting the onset of atrial fibrillation (AF, an arrhythmia resulting in an elevated HR) [217, 218], and tracking the progression of sepsis (an over-reaction to an infection) [219–222]. More broadly, it is reduced in critical illness, and restored during recovery from illness (such as after cardiac surgery) [223–225]. Its inclusion in an EWS has been beneficial for prediction of cardiac arrest [130]. Software is freely available for its calculation [226, 227].

- *Photoplethysmographic Variability (PPGV)*

  Preliminary studies have shown the utility of PPGV in diagnosing sepsis [211, 215, 228], acute coronary syndromes [229], and blood loss [230].

- *Additional ECG metrics*

  Similarly to PPGV, the frequency content of the ECG changes between normal and disease states [231]. Individual ECG features have been used to predict AF, as reviewed in [232]. Since this review, methods have been trialled on cardiac post-operative patients [233–235], and are ongoing [236, 237]. Arrhythmias are routinely detected using the ECG [238].

- *Measures of vascular tone and arterial stiffness*

  The stiffness and reflection indices, derived from the PPG, quantify arterial stiffness and vascular tone respectively [239, 240].

- *Approximate central BP*

  Central pressures are more indicative of cardiovascular risk than peripheral pressures [241–243]. Central pulse pressure can be estimated from the peripheral augmentation index [244]. When using the PPG, the Stiffness Index must be used to approximate the augmentation index [245]. Central pulse pressure could then be estimated using a routine BP measurement for calibration. If the PPG is assumed to be a function of arterial diameter, then it can be modelled as the windkessel (or reservoir) pressure, giving rationale for using it to calculate augmentation index [246].

- *Quality of sleep*

  Although not strictly indicative of cardiovascular state, quality of sleep can be estimated from an ECG signal, and may well indicate physiological state indirectly [247]. The oxygen desaturation index (number of desaturation episodes per hour), also indicates quality of sleep [248], and is predictive of AF [249].

These parameters have not yet been used to calculate physiological trajectories.

The ABP signal is influenced by the heart and vasculature, and could be used to monitor cardiovascular response to surgery, as it is monitored for approximately 24 hours after surgery. Two indices of cardiovascular function are proposed:

- *Cardiac Output (CO)*

  CO, the volume of blood pumped in one minute:

$$\text{Cardiac Output } (Lmin^{-1}),\ CO = \frac{60}{T}\int_0^T Q_{in}\mathrm{d}t \tag{4.1}$$

  where Q_{in} is the flow of blood, and t is time, is relevant in this population given: (i) the incidence of congestive heart failure (11% of complications [150]); (ii) the importance of monitoring CO in critical care; and, (iii) recent research into the role of CO monitoring to guide delivery of fluids and inotropes (drugs which alter the force of myocardial contraction) during cardiac surgery for the prevention of post-operative complications (the *'Optimise'* study, National Clinical Trial 01775735).

- *Cardiac Excess Work*

  Cardiac excess work (the excess work beyond the minimal work required to pump a given stroke volume) has recently been proposed as an early indicator of chronic cardiac events [250, 251]. If the excess pressure is assumed to be proportional to flow then excess work can be approximated using ABP [252]. Excess work then becomes a function of CO (when CO is calculated in a novel manner, using the excess pressure).

CO is required for calculation of both indices. It is not routinely monitored post-cardiac surgery, so would need to be estimated from the ABP signal in LISTEN. We have previously shown that CO monitors are imprecise during changes in vascular tone (a frequent occurrence postoperatively due to administration of vasoactive drugs) [253, 254]. Therefore, we sought to evaluate

the ability of CO algorithms to trend precisely during changes in vascular tone. If an algorithm is sufficiently precise, this will facilitate calculation of these cardiovascular markers for detection of deteriorations.

4.3 Methodology

We will identify the most precise CO algorithm in three steps:

1. Derivation of CO algorithms from first principles to identify the underlying assumptions.
2. Evaluation of the precision of CO algorithms during changes in vascular tone. Data from a previous study was used [254]. Briefly, ABP signals were acquired alongside reference CO measurements (transpulmonary thermodilution CO, TPTDCO, measurements) from 15 ICU patients during a norepinephrine 'double-pumping' manoeuvre (shown in Figure 4.2). Continuous CO was calculated retrospectively using each algorithm, and scaled to make the mean continuous CO during the 'before' TPTDCO equal to that TPTDCO (the *"first point"* methodology in [255]). We used the range of statistical parameters suggested by Papaioannou *et al.* to assess precision [256].
3. The most precise CO algorithm will be identified, and the conditions in which it can be expected to be precise will be determined from its underlying assumptions.

4.4 Preliminary Results

Initial results of the first two steps are presented here.

4.4.1 Derivation of CO Algorithms

The nomenclature used in CO algorithms is given in Table 4.2 and illustrated in Figure 4.3. The algorithms are listed in Table 4.4. Those algorithms which have been derived are above the solid line, and those which have been implemented are in bold.

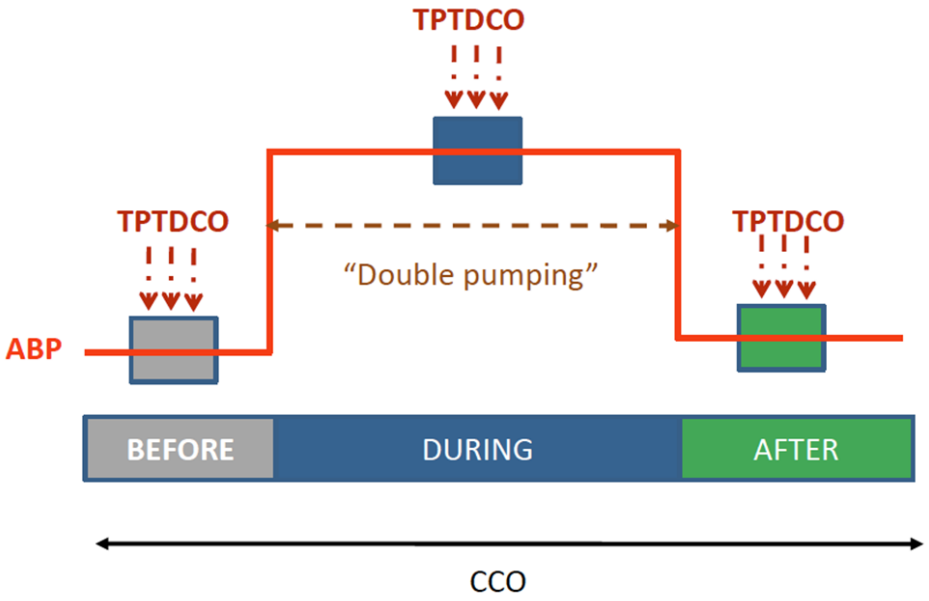

FIGURE 4.2: Norepinephrine 'double-pumping' manoeuvre. ABP signals (red line) were continuously recorded during the manoeuvre, in which the dosage of vasopressor (Norepinephrine) was doubled for approximately 15 minutes. Reference TPTDCO measurements were performed in triplicates (arrows) before (grey area), during (blue area) and after (green area) the manoeuvre. Copied from [257]

TABLE 4.2: ABP nomenclature

	Definition
P	ABP signal
P_s	Systolic Pressure
P_d	Diastolic Pressure
P_z	Pressure at Dicrotic Notch
P_p	Pulse Pressure: $P_s - P_d$
P_{md}	Mean Distending Pressure
T_s	Duration of Systole
T_d	Duration of Diastole
T	Duration of pressure pulse: $T_s + T_d$
P_m	Mean Pressure: $\frac{1}{T}\int_T P(t)\mathrm{d}t$
A_{sys}	Systolic Area: $\int_0^{T_s} P(t)\mathrm{d}t$
A_{dia}	Diastolic Area: $\int_{T_s}^{T} P(t)\mathrm{d}t$
V_{in}	Stroke Volume
HR	Heart Rate: $60/T$
CO	Cardiac Output: $V_{in}.HR$
$q(t)$	Arterial Blood Flow waveform
R	Systemic Vascular Resistance
τ	Diastolic Decay Time Constant

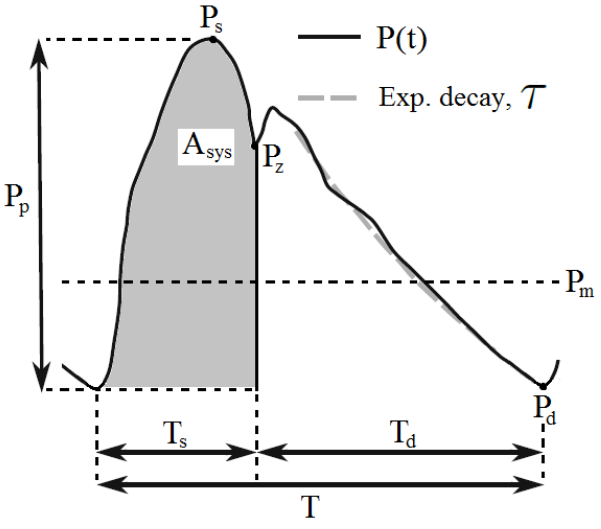

TABLE 4.3: Aortic pressure waveform, illustrating the nomenclature used in Table 4.2 (modified from [258]).

TABLE 4.4: Cardiac Output Algorithms

Algorithm name	Formula	Citation	Comparison studies
Mean Arterial Pressure	$SV \quad \alpha \quad P_m$	[255]	[255] [259]
Mean Arterial Pressure RC Decay	$SV \quad \alpha \quad P_m \ln \frac{P_s}{P_d}$	[260]	[255]
Pulse Pressure	$SV \quad \alpha \quad P_p$	[261]	[262] [255] [259] [256]
Pulse Pressure by L and Z	$SV \quad \alpha \quad \frac{(P_p)}{(P_s+P_d)}$	[263]	[255] [259] [256]
Diastolic Pressure across Systole	$SV \quad \alpha \quad P_z - P_d$	[262]	[262]
Systolic Area	$SV \quad \alpha \quad A_{sys}$	[262]	[262] [255] [259] [256]
Distending Pressure	$SV \quad \alpha \quad P_{md}$	[262]	[262]
Modified Pulse Pressure by L and Z	$SV \quad \alpha \quad \frac{(P_p)}{(P_m)}$	[255]	[255]
Pulse Pressure corrected ratio	$SV \quad \alpha \quad P_p.(1 + \frac{T_s}{T_d})$	[262]	[262]
Diastolic Pressure Difference corrected ratio	$SV \quad \alpha \quad (P_z - P_d).(1 + \frac{T_s}{T_d})$	[262]	[262]
Systolic Area corrected ratio	$SV \quad \alpha \quad A_{sys}.(1 + \frac{T_s}{T_d})$	[262]	[262] [255] [256]
Distending Pressure corrected ratio	$SV \quad \alpha \quad P_{md}.(1 + \frac{A_{sys}}{A_{dia}})$	[262]	[262]
Herd	$SV \quad \alpha \quad P_m - P_d$	[264]	[255] [259] [256]
Harley	$SV \quad \alpha \quad (P_p).T_s$	[265]	[256]
Bourgeois	$SV \quad \alpha \quad (P_z - P_d) + \frac{A_{sys}}{\tau}$	[266]	[256]
Wesseling	$SV \quad \alpha \quad A_{sys}.(163 + HR - 0.48P_m)$	[262]	[255] [259] [256]
Power	$SV \quad \alpha \quad \sqrt{\frac{1}{T}.\int_t (P(t) - P_m)^2 dt}$	[267]	[256]
eSVB	$SV \quad \alpha \quad (P_p).C$	[267]	[256]
Power II	$SV \quad \alpha \quad \sqrt{\int_t (P(t) - P_m)^2 dt}$	[255]	[255]
Godje	$q(t) \quad \alpha \quad \frac{1}{R}(P(t) + \frac{P_m^3}{3P_m P(t) - 3P_m^2 - P(t)^2} \cdot \frac{dP(t)/dt}{\lvert dP(t)/dt \rvert})$	[268]	[255]
Wesseling	$Modelflow$	[269]	[255]

General Equation for Flow

In 1899, Frank applied the Windkessel model (Figure 4.3) to ABP to derive a general expression for CO [270]. He made the following assumptions:

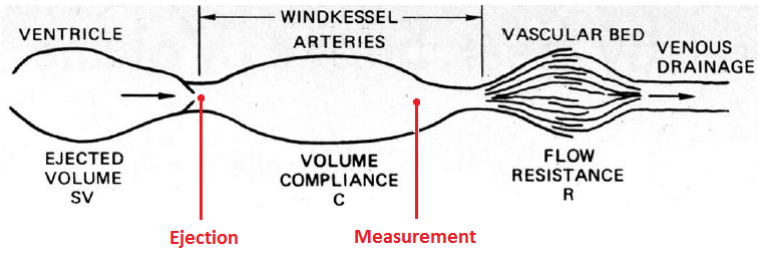

FIGURE 4.3: The Windkessel Arteries (modified from [271]), showing the points of ejection of stroke volume, and measurement of ABP.

- No wave reflections
- Laminar flow
- Pressure is equal throughout the large arteries (i.e. pulse wave velocity is instantaneous).

He used conservation of mass in an elastic fluid-carrying tube, as shown in Figure 4.4, with the equivalent electrical circuit in Figure 4.5.

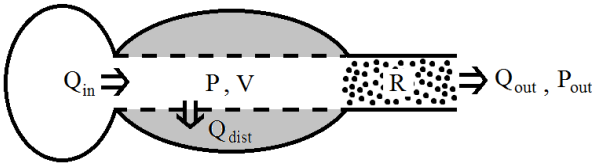

FIGURE 4.4: Flow in, Q_{in}, out, Q_{out}, and distending, Q_{dist}, of an elastic tube containg a volume V of fluid at uniform pressure P.

Q_{dist} and Q_{out} can be expressed using functions for compliance and outflow as:

Distending flow:
$$Q_{dist} = \frac{dV}{dt} = \frac{dV}{dP}\frac{dP}{dt} \tag{4.2}$$

Compliance:
$$\frac{dP}{dV} = f(P) \tag{4.3}$$

$$\therefore Q_{dist} = \frac{1}{f(P)}\frac{dP}{dt} \tag{4.4}$$

Outflow:
$$Q_{out}(t) = \varphi(P) \tag{4.5}$$

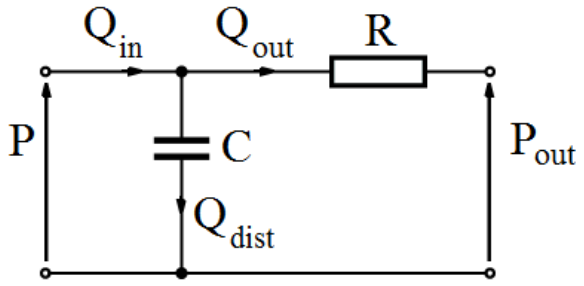

FIGURE 4.5: The equivalent electrical circuit model for flow in an elastic vessel (adapted from [272]).

Using conservation of mass, inflow to the elastic tube, Q_{in}, can be expressed as:

$$\text{Inflow:} \quad Q_{in}(t) = Q_{dist}(t) + Q_{out}(t) \tag{4.6}$$

$$= \frac{dV}{dP}\frac{dP}{dt} + \varphi(P) \tag{4.7}$$

$$= \frac{1}{f(P)}\frac{dP}{dt} + \varphi(P) \tag{4.8}$$

Stroke volume is defined as:

$$\text{Stroke Volume:} \quad V_{in} = \int_0^T Q_{in} dt \tag{4.9}$$

Substituting for Equation 4.8 into Equation 4.9 gives a general equation for stroke volume:

$$\text{Stroke Volume:} \qquad V_{in} = \frac{dP}{f(P)} + \varphi(P)dt \qquad \text{(CO Algorithm 1: General)}$$

Individual CO algorithms can be derived from this general equation by imposing additional assumptions.

Mean Arterial Pressure

The following additional assumptions are made to derive this CO algorithm, including conservation of momentum:

$$\text{Periodic flow:} \qquad P(T) = P(0) \tag{4.10}$$

$$\text{Outflow determined by Poiseuille's law:} \qquad \varphi(P) = \frac{P - P_{out}}{R} \tag{4.11}$$

$$\text{Asymptotic Pressure:} \qquad P_{out} = 0 \tag{4.12}$$

where P_{out} is the arterial pressure at which flow through the microcirculation stops. Substituting into CO Algorithm 1: General:

$$V_{in} = \frac{1}{f(P)} \int_0^T \mathrm{d}P + \int_0^T \frac{P}{R}\,\mathrm{d}t \tag{4.13}$$

$$V_{in} = \frac{1}{f(P)}(P(T) - P(0)) + \frac{1}{R}\int_0^T P\,\mathrm{d}t \tag{4.14}$$

$$V_{in} = \frac{T}{R}P_m \qquad \text{(CO Algorithm 2: } P_m\text{)}$$

Chen noted that this is "*valid only for time-averaged flow and not intra-beat fluctuations*" [259].

Mean Arterial Pressure RC decay

In addition to the assumptions made to derive CO Algorithm 2: P_m, the following assumption is made to derive this CO algorithm:

$$\text{Compliance is constant:} \quad f(P) = \frac{1}{C} \tag{4.15}$$

Rearranging Equation CO Algorithm 2: P_m gives: [255]

$$V_{in} = \frac{T}{R}P_m = \frac{TC}{RC}P_m = \frac{TC}{\tau}P_m \tag{4.16}$$

Sun [255] reported that if it is assumed that ejection is instantaneous (i.e. it can be represented by a train of Dirac delta functions, as shown in Figure 4.6) then the whole cardiac cycle is in exponential decay, and the third CO algorithm can be derived:

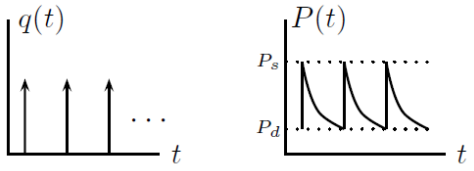

FIGURE 4.6: Flow waveform represented by a Dirac delta function. (modified from [255])

$$P_d = P_s e^{\frac{-T}{\tau}} \tag{4.17}$$

$$\tau = \frac{T}{\ln \frac{Ps}{Pd}} \tag{4.18}$$

Substituting into Equation 4.16:

$$V_{in} = CP_m \ln \frac{Ps}{Pd} \qquad \text{(CO Algorithm 3: } P_m \text{ RC decay)}$$

Sun also obtained τ by "*fitting a least squares fit of an exponential decay to the diastole portion of the ABP waveform*" [255].

Pulse Pressure

Westerhof et al. summarised the derivation of the Pulse Pressure algorithm [258]. The following assumptions are made:

Compliance is constant: $$f(P) = \frac{1}{C} \qquad (4.19)$$

Outflow is zero (infinite peripheral resistance): $$\varphi(P) = 0 \qquad (4.20)$$

If $\varphi(P) = 0$, then $P(t)$ will be highest at the end of ejection (T_s). Since outflow is not zero in reality, a lower maximum pressure of P_s is reached between $t(0)$ and T_s. Therefore, $dP = \Delta P = P_{max} - P(0) \approx P_p$. Substituting into Equation CO Algorithm 1: General:

$$V_{in} = C.P_p \qquad \text{(CO Algorithm 4: } P_p\text{)}$$

However, Westerhof et al. noted that since in reality some of the stroke volume leaves through the periphery, this underestimates stroke volume [258]. A second explanation was given by Sun based on the assumption of instantaneous ejection [255].

Sun gave an alternative derivation, based on the following assumptions [255]:

Compliance is constant: $$f(P) = \frac{1}{C} \qquad (4.21)$$

Ejection is instantaneous: $$T_s = 0 \qquad (4.22)$$

Instantaneous ejection implies that flow can be represented by a train of Dirac delta functions, as shown in Figure 4.6 [255].

In contrast to the previous derivation, the result of these assumptions in that the maximum pressure (again, P_s) occurs at $t = 0$, giving the same expression for V_{in}.

Pulse Pressure by Liljestrand and Zander

Liljestrand and Zander suggested the following empirical formula for stroke volume:

$$V_{in}\,\alpha\,\frac{2P_p}{P_d+P_s} \qquad \text{(CO Algorithm 5: } P_p \text{ Liljestrand)}$$

This can be obtained by replacing the assumption of constant compliance ($f(P)=\frac{1}{C}$) with $f(P)=P_d+\frac{P_p}{2}$ in Equation CO Algorithm 4: P_p [263]. The authors noted that this was less precise than the expression proposed by Fürst and Soetbeer: $f(P)=P_d+\frac{P_p}{3}$ [273].

Pulse Pressure across Systole

Warner et al. stated the systolic pressure difference algorithm, but did not give a derivation [262]. The derivation is as for Equation CO Algorithm 4: P_p, except the assumption of no outflow is maintained, and therefore it is assumed that pressure is at a maximum at the end of sytole. Therefore, P_p is replaced with P_z-P_d:

$$V_{in}=C.(P_z-P_d) \qquad \text{(CO Algorithm 6: } P_p \text{ Systole)}$$

Systolic Area

Warner et al. also stated the systolic area algorithm, but did not give a derivation [262]. Kouchoukos et al. [274] believed that the algorithm originated from Frank's work in 1930 [275]. The following assumptions are made:

No compliance: $$f(P)=\infty \tag{4.23}$$

Outflow determined by Poiseuille's law: $$\varphi(P)=\frac{P-P_{out}}{R} \tag{4.24}$$

Zero flow in diastole: $$Q_{in}(t)=\begin{cases} Q_{in}(t) & \text{during systole,} \\ 0 & \text{during diastole.} \end{cases} \tag{4.25}$$

Using Equation CO Algorithm 1: General:

$$Q_{in} = \frac{1}{R}\int_0^T P\mathrm{d}t \tag{4.26}$$

$$Q_{in} = \frac{1}{R}\int_0^{T_s} P(t) - P_{out}(t)\mathrm{d}t \qquad \text{(CO Algorithm 7: SA)}$$

Here, the period of interest is reduced to systole, since for a non-compliant vessel $P(t) = 0$ when $Q_{in}(t) = 0$. To calculate stroke volume, a further assumption has to be made about the nature of $P_{out}(t)$. For instance:

$$P_{out}(t) = P_d \quad [274] \Rightarrow \qquad Q_{in} = \frac{1}{R}\int_0^{T_s} P(t) - P_d\,\mathrm{d}t \tag{4.27}$$

Distending Pressure

Warner et al. derived the distending pressure algorithm without referring to the Windkessel model [262]. Since their publication gives a very thorough derivation, it is only outlined below. They assumed:

$$\text{Compliance is linear:} \qquad f(P) = \frac{1}{C} \tag{4.28}$$

In the following equations, the "*volume of blood draining from the arterial bed during systole*" is denoted as S_d, whilst that during diastole is D_d. The end-systolic uptake, U, is the "*increment in the volume of the arterial bed ... at the end of sysole*" compared to the end of diastole.

$$Q_{in} = S_d + D_d \tag{4.29}$$

$$= S_d + U \tag{4.30}$$

Since compliance is linear:

$$\frac{A_{sys}}{S_d} = \frac{A_{dia}}{D_d} \tag{4.31}$$

$$U = C.(P_z - P_d) \tag{4.32}$$

$$\therefore Q_{in} = C.(P_z - P_d).(1 + \frac{A_{sys}}{A_{dia}}) \qquad \text{(CO Algorithm 8: DP)}$$

Here, the authors' definition of the distending pressure has been modified slightly.

4.4.2 Evaluation of CO Algorithms

The 15 patients had an age of 54 ± 28 years (med ± iqr), and 9 were male. Details of the recording periods are given in Table 4.5.

TABLE 4.5: Intervention Characteristics

	Before	During	After
Period Duration / s , med ± iqr	523 ± 95	663 ± 478	1193 ± 1034
Bolus Duration / s , med ± iqr	195 ± 75	188 ± 132	176 ± 142
Bolus CO / l/min , med ± iqr	6.6 ± 2.5	7.4 ± 3	6.4 ± 2.6

Results are given for the during and after periods in Tables 4.6, and 4.7 (Coefficient of Determination - R sq, Mean Difference, Coefficient of Variation, RMSE, Limits of Agreement - LOA).

TABLE 4.6: Precision of CO algorithms during change in vascular tone

	R sq	**Mean Diff ± SD**	**Coeff of Var**	**RMSE**	**LOA**
Mean Arterial Pressure	0.48	1.5 ± 1.1	0.72	1.8	0.4, 2.5
Mean Arterial Pressure RC decay	0.21	2.1 ± 1.5	0.71	2.6	0.6, 3.6
Pulse Pressure	0.21	2.1 ± 1.5	0.72	2.5	0.6, 3.5
Pulse Pressure by L and Z	0.39	1.1 ± 0.8	0.76	1.4	0.3, 2.0
Systolic Area	0.16	2.8 ± 4.0	1.40	4.8	-1.2, 6.8
Mod. Pulse Pressure by L and Z	0.42	1.0 ± 0.8	0.78	1.3	0.2, 1.8
Herd	0.29	2.1 ± 1.7	0.80	2.7	0.4, 3.9
Wesseling	0.22	2.4 ± 2.6	1.10	3.6	-0.2, 5.1

TABLE 4.7: Precision of CO algorithms after change in vascular tone

	R sq	**Mean Diff ± SD**	**Coeff of Var**	**RMSE**	**LOA**
Mean Arterial Pressure	0.67	0.66 ± 0.54	0.82	0.85	0.12, 1.2
Mean Arterial Pressure RC decay	0.56	0.87 ± 0.73	0.85	1.1	0.13, 1.6
Pulse Pressure	0.54	0.87 ± 0.76	0.87	1.1	0.11, 1.6
Pulse Pressure by L and Z	0.66	0.65 ± 0.7	1.1	0.94	-0.048, 1.3
Systolic Area	0.28	1.2 ± 2.2	1.9	2.5	-1, 3.4
Mod. Pulse Pressure by L and Z	0.63	0.69 ± 0.75	1.1	1	-0.06, 1.4
Herd	0.58	0.84 ± 0.72	0.86	1.1	0.12, 1.6
Wesseling	0.32	1.2 ± 2.2	1.8	2.5	-1, 3.5

Eight algorithms were implemented. All algorithms were more precise after return to baseline vascular tone.

4.5 Discussion and Conclusions

We have identified parameters which could be implemented on the LISTEN data to indicate cardiovascular state. Those which are derived from ECG and PPG signals, and could be used to detect deteriorations, have not yet been implemented. However, software is available for calculation of HRV and PPGV allowing straightforward implementation. Since these have been widely cited as predictors of cardiovascular events, this should be the next step. In addition, calculation of the stiffness index may be beneficial given its utility in tracking chronic disease. Use of the stiffness index to estimate central pulse pressure may be possible, given that the stiffness index has been calculated previously in similar age groups [210]. However, the increased arterial stiffness often encountered in a cardiac population may preclude identification of the diastolic peak.

Eight CO algorithms have been derived using the Windkessel model. This will allow critical appraisal of their underlying assumptions. Eight CO algorithms have been evaluated during a change in vascular tone. The remaining algorithms should be implemented, since these are largely the more modern algorithms. In addition, further analysis is required to determine the most precise algorithm. An understanding of the algorithms' precisions and underlying assumptions will allow us to decide whether it is reasonable to apply an algorithm to the LISTEN data. Results would be used as a predictor variable for the class of physiological trajectory.

Chapter 5

Conclusions and Future Work

5.1 Summary and Key Findings

Although an EWS has been recommended for monitoring of acutely-ill inpatients throughout the NHS, evidence suggests that it is at best a late indicator of clinical deterioration. The introduction of electronic documentation of physiological parameters provides opportunity to apply more sophisticated algorithms to improve its performance. The aim of this PhD is to develop physiological trajectory analyses for prediction of deteriorations earlier than current practice.

Chapter 1 detailed the prior art of detection of deteriorations, including both current practice and techniques developed for electronic analysis. We also outlined the clinical contexts in which physiological trajectories have been calculated, and the mathematical techniques used to do so. We proposed detecting deteriorations from physiological trajectories by: (i) identifying the class of trajectory which a patient is following; (ii) assessing dynamic behaviour of trajectories; and, (iii) using a patient-specific model of normality.

Chapter 2 outlined the methodology used to construct a comprehensive and annotated physiological database on which to develop and test algorithms for predicting deteriorations. Data has been collected from 226 post-cardiac surgery patients using both bedside and portable monitors to ensure coverage throughout their hospital stay. An effective algorithm was designed for correction of timestamps on this data to provide data suitable for analysis. With have implemented beat detection and SQI algorithms on ECG and PPG data to eliminate parameters derived from

poor quality data. Preliminary trajectories were calculated using Kernel Density Estimation to quantify physiological state, and Gaussian Processes to calculate trajectories.

Chapter 3 detailed seven methods which have been proposed for estimating RR continuously from the PPG and ECG. We have implemented three of these on data collected from young and elderly volunteers, tested on signals recorded from bespoke high resolution equipment, and from routine monitoring equipment. Autoregressive algorithms were most precise.

Chapter 4 considered additional indices of cardiovascular function derived from continuous signals. We proposed that these could be used to detect deteriorations, and, when acquired using invasive measurements early in a patient's recovery, as predictor variables of the class of trajectory which a patient will follow. We have derived several CO algorithms from the windkessel model to understand their underlying assumptions. The precision of these algorithms was assessed during changes in cardiovascular state, with no algorithm performing sufficiently well across the population for precise calculation of cardiovascular indices.

5.2 Future Work

The remaining work required to test the hypothesis is:

1. *Evaluation of RR algorithms*

   Evaluation of the precision of RR algorithms should be completed, incorporating the additional metrics used to evaluate CO algorithms. Additional techniques should be included in the analysis. Patient data recorded in LISTEN from patients for the hours before leaving HDU should be used to evaluate the algorithms in a patient population, using quality-checked RRs derived from thoracic electrical impedance as a reference. The optimal algorithm should then be implemented for calculating physiological trajectories.

2. *Evaluation of cardiovascular parameters*

   Evaluation of the precision of CO algorithms should be completed, implementing the more complex algorithms which have been omitted so far. HRV, PPGV and stiffness index parameters implemented on the LISTEN data.

3. *Variability analyses*

   The suggested variability indices should be incorporated, and trajectories calculated at

different time scales. This will ensure full utilisation of the temporally rich data available to calculated trajectories.

4. *Calculation of physiological trajectories*

   Parameters which change during deteriorations should be identified, and retained for calculation of physiological trajectories. All others should be excluded. A multi-dimensional Kernel Density Estimate should be implemented for more accurate calculation of physiological state. Classes of trajectories should be identified using growth mixture modelling, according to (i) patient type, and (ii) complication type. Deteriorations should then be predicted using Gaussian process and growth mixture models. Appropriate statistics should be used to evaluate their performance (as described in [276]). Deteriorations could be defined as: (i) deteriorations annotated by researchers; or, (ii) periods of instability. We have set up a collaboration with the Neurological ICU at the Southern General Hospital, Glasgow, to evaluate the performance of trajectories on their continuous data in a very different setting.

5. *Recommendations for clinical practice*

   The continuous estimates of 3 NEWS parameters post-cardiac surgery could be decimated[1] to determine the theoretical benefit of monitoring NEWS at higher frequencies. The performance of parameters outside of NEWS should be investigated. These conclusions could inform clinical practice.

5.2.1 Targets

The work required can largely be conducted in parallel. There is also much redundancy, since if specific parameters, variability analyses, or modelling methods for calculating trajectories are omitted then it will still be possible to test the hypothesis. Figure 5.1 shows the planned timetable of work.

[1] reducing sampling frequency whilst maintaining low frequency information

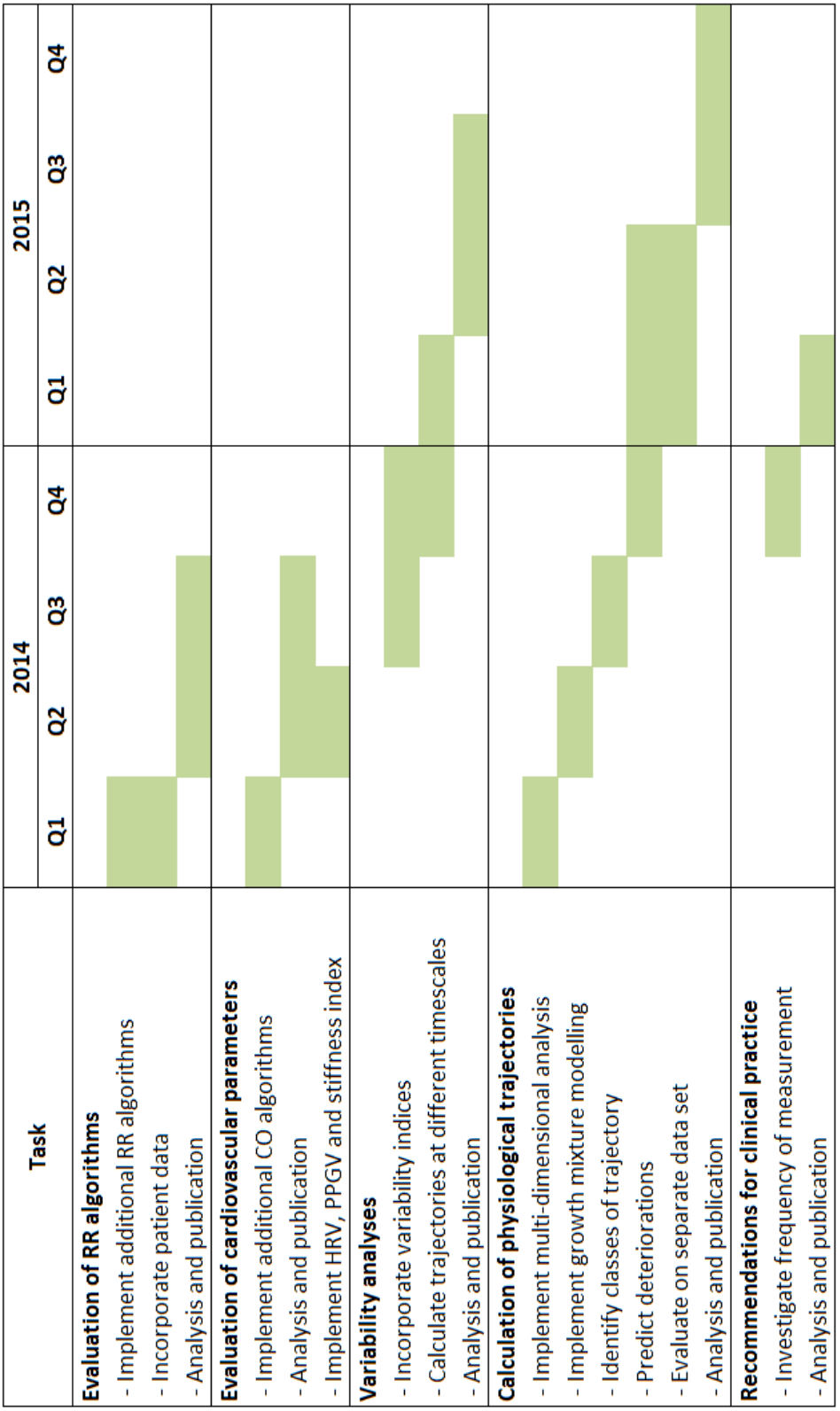

FIGURE 5.1: Proposed stages of work.

Appendix A

A history of Early Warning Scores

A brief overview of the major developments in EWSs is given in Table A.1:

TABLE A.1: Major developments in EWSs.

Year	Development
1995	Physiological scoring criteria proposed to identify patients at risk of deterioration [21].
1997	Morgan *et al.* presented the first EWS [277].
2000	The original EWS was modified by Stenhouse, giving a modified EW score (MEWS) *et al.* [278].
2001	MEWS was validated in a medical (rather than surgical) patient population [279].
2007	The National Institute for Health and Clinical Excellence (NICE) recommended that EWSs should be used to monitor all adult patients in acute hospital settings [280].
2010	The VitalPAC EWS (ViEWS) was developed based on a large vital signs database [23].
2011	The first EWS derived from statistical distributions of vital signs was developed [71].
2012	The NHS EWS (NEWS) was developed based on expert modification of ViEWS, and recommended for use across the NHS by the Royal College of Physicians [6].

Appendix B

Evidence for the physiological parameters used in NEWS

The NEWS input parameters were recommended by the National Institute for Health and Clinical Excellence (NICE) [280], and confirmed by a consensus conference [20]. An exception, supplemental oxygen, was added based on evidence in [23]. It is essential that the NEWS input parameters are early indicators of deterioration [22]. Table B.1 summarises the evidence for this.

TABLE B.1: Physiological inputs to NEWS

Parameter	Evidence
Respiration Rate (RR)	Abnormal RR precedes cardiac arrest [14, 154, 281, 282], and elevated RR indicates respiratory dysfunction [283]. Both elevated and reduced RR ($\geq$ 20 and <6 breaths per min, bpm) predict mortality [17, 284, 285]. RR has been shown to be a particularly important indicator of deterioration. For instance, it has been observed to be the best discriminator of patient risk [29]; to be the best single variable predictor of cardiac arrest [26]; and, to be highly predictive (odds ratio, OR = 9.1 for RR >24 bpm) of resuscitation events and death [19].
Blood Oxygen Saturation (SpO2)	Reduced SpO2 is a risk factor for cardiac arrest [282], a predictor of mortality [284, 285], and precedes critical conditions [49].
Temperature (temp)	Abnormal temp is a risk factor for cardiac arrest [282] and mortality [284]. However, some studies have shown otherwise [22, 286, 287].
Systolic BP (SBP)	SBP is a risk factor for cardiac arrest [36, 282], and a predictor of mortality [17, 284, 285].
Heart Rate (HR)	Both tachycardia (elevated HR) and bradycardia (reduced HR) are predictors of caridac arrest and mortality [282, 284, 285].
Level of Consciousness (LOC)	A wide range of changes in mental function may precede cardiac arrest [14, 36]. A decrease in Glasgow Coma Score (GCS) by two points, the onset of coma, or disturbed consciousness are associated with an increase in the risk of mortality [284, 285].
Administration of supplemental oxygen	Patients can be provided with supplementary oxygen to increase the concentration of oxygen in inspired air.

Appendix C

Continuous Data Processing

C.1 Formatting

XML files were obtained from BedMaster's proprietary STP file format using *STPtoXML.exe v.5* (Excel Medical Electronics). The data in these XML output files is timestamped each second. An example is shown below:

Time = 1355316071

HR = 60

ECG = [-0.250, -0.251, -0.250, -0.276, -0.304, ...]

Since numerics are given at 1 Hz, and waveforms at 125 Hz, each timestamp is followed by one value for each recorded numeric, and a vector of 125 samples of each recorded waveform. Physiological data from the XML files were converted to Matlab format for data processing.

C.2 Processing

C.2.1 Removal of false data

Data was only imported if the patient was being monitored by that monitor at the recorded time. [1] All other data was discarded. Monitored variables were converted to a structure containing

[1] The eCRF was used to determine whether a patient was being monitored by a particular monitor at a given time. The patient's location (bed number and ward) was recorded in the eCRF, and when they were being

outputted values and corresponding times.

The following rules were used to remove false data:

1. Any value of 8388607 (BedMaster's equivalent of a NaN) was discarded.
2. Any value of greater than 1×10^9 was discarded.
3. The first timestamp in each XML file was 01/01/1970.[2] These timestamps and associated data were discarded.

monitored by telemetry, the label of their telemetry device was recorded. Since bedside monitors were labelled according to the bedspace in which they permanently resided, this information was sufficient.

[2] BedMaster uses the Coordinated Universal Time

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